Allylation of glycine equivalents during solid phase peptide synthesis

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Allylation of glycine equivalents during solid phase peptide synthesis

by

David Richard Holland

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Abstract

This thesis contains research into the development of methodology for the palladium catalysed allylation of glycine equivalents during solid phase peptide synthesis. The attempted synthesis of oxazoline ligands attached to solid supports is also included.

The research into the palladium catalysed allylation of glycine equivalents during solid phase synthesis was conducted in the following manner:-

Firstly, a solution phase model study was performed in which the allylation of simple dipeptides was investigated. Various bases and activating groups were used to determine which was the most suitable for the reaction. It was found that a phosphazene base was the most suitable base and that an imine derived from benzophenone imine was the most suitable activating group. This is because of the strong basicity of phosphazene bases and the stability of imines derived from benzophenone imine.

Secondly, the reaction was applied to solid phase chemistry. Optimisation of the reaction using different resins, ligands, bases and solvents was investigated. The allylation of glycine equivalents attached to 2-trityl chloride and TGR resins was successfully carried out. In addition the palladium catalysed allylation of glycine equivalents during liquid phase peptide synthesis was investigated but without success.

Thirdly, imines derived from fluorenone imine were synthesised to find out if they could be used to improve the reliability and scope of the reaction during solid phase peptide synthesis. To this end fluorenone imine was synthesised from 9-hydroxy fluorenone. Unfortunately, however, in solution phase chemistry model studies it was not possible to allylate these imines, so this area of research was not pursued further.

An attempt to synthesis oxazolines ligands attached to resins was also carried out but unfortunately it proved unsuccessful.

Abbreviations

Ar	Aromatic
^{t}boc	Tertiary-Butoxycarboimide
BEMP	2-*tert*-Butylimino-2-diethylamine-1,3-dimethylperhydro -1,3,2-diazaphosphorine
Bu	Butyl
ChloroTrCl	2 Chloro trityl chloride resin
DMF	Dimethylformamide
DIPCDI	Diisopropyl carbodiimide
de	Diastereoisomeric excess
ee	Enantiomeric excess
Et	Ethyl
Fmoc	9-Fluorenylmethyoxycarboimide
HOBT	1-Hydroxy-1H-benzotriazole hydrate
HOAt	1-Hydroxy-7-azabenzotriazole
NMR	Nuclear magnetic resonance
Me	Methyl
Ph	Phenyl
$Pd_2(dba)_3$	Tris(dibenzylideneacetone) dipalladium (0).
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TGR	Tentagel Rink amide resin
●	Solid support
THF	Tetrahydrofuran
tlc	Thin layer chromatography

Contents

Chapter 1

A brief introduction to solid phase peptide synthesis - its background, advantages, scope and limitations.

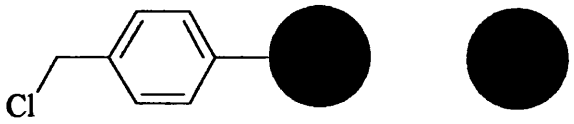
(i) Background

Solid phase peptide synthesis has been used for over thirty years, since Merrifield synthesised L-Leu-L-Ala-Gly-L-Val-OH using Merrifield resin **1** as his solid support.[1] The basic structure of resins is a solid support and a linker. The linker is the part of the molecule which has a functional group to which the amino acid can be attached, for example benzyl chloride in resin **1**. In Merrifield resin **1** polystyrene was the support for the linker. Today many resins are based on Tentagel, a composite of polyethylene oxide grafted on to a low cross-linked polystyrene gel-type matrix, which has been amino functionalised and derivatised with the TFA labile 4-hydroxymethylphenoxyacetic acid linker. The advantages of solid phase peptide synthesis are three fold :

(i) when synthesising a long chain peptide by classical methods the technical difficulties associated with solubility and purification become more formidable the longer the chain becomes. If the growing peptide chain is firmly attached to a completely insoluble solid particle it is in a convenient form to be filtered and washed free of reagents and by-products.[1]

(ii) The reactions can be automated more easily than solution phase chemistry as the whole reaction sequence takes place in one container.[2]

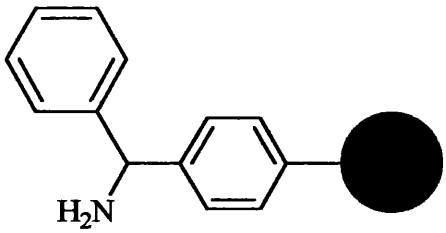
(iii) As solid phase chemistry can be automated, it is possible to run a wide range of reactions in parallel. This enables the generation of a large number of structurally similar but different peptides, by making one or two changes in a key step. When a research group wants to work out which peptide will bind most efficiently to a biological receptor or which amino acids are responsible for binding to a receptor in a peptide chain, this approach can save time.



= solid support (in this case polystyrene)

Merrifield resin **1**

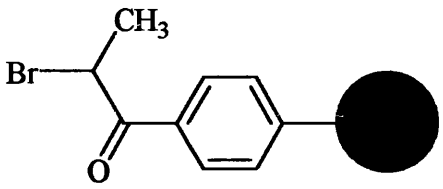
The original work carried out by Merrifield used carbobenzoyloxy amino acids and either 10% HBr/30% HBr or HBr/NaOH for the deprotection and cleavage of the peptide chain. Later work used ^{t}Boc amino acids with TFA/HF for the deprotection and cleavage of the peptide chain.[3] Despite the synthesis of other resins that enable TFA/HF or Pd/H_2 to be used for the deprotection and cleavage of the peptide chain e.g. in MBHA (2),[3] alternative synthetic strategies have been investigated. This is because of the toxicity of HF, the non-specificity of Pd/H_2 which can damage other functional groups e.g. double bonds in the peptide molecule, and concern that repetitive TFA acidolysis could cause acid catalysed side reactions.



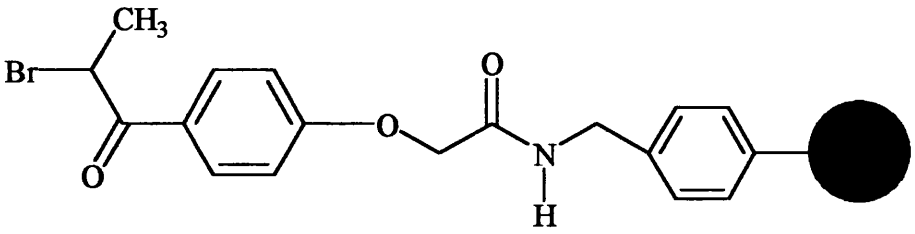
MBHA **2**

(ii) Different linkers

One alternative strategy has been the use of resins that can be cleaved by the use of photolysis e.g. Br-Wang **3** and Br-PPOA **4**.[4,5]

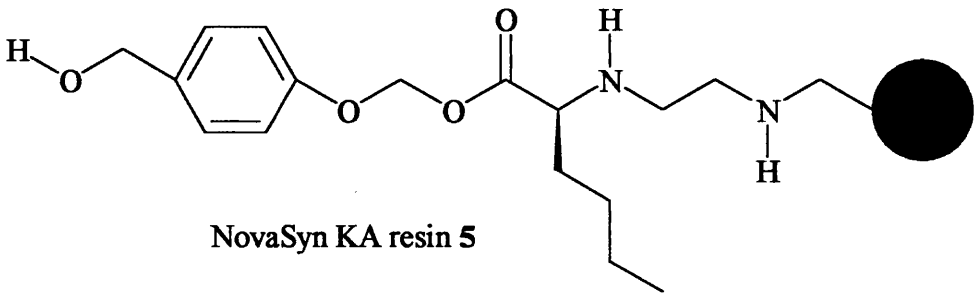


Brominated Wang resin **3**

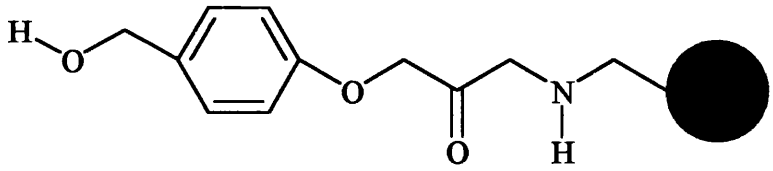


Br-PPOA Wang resin **4**

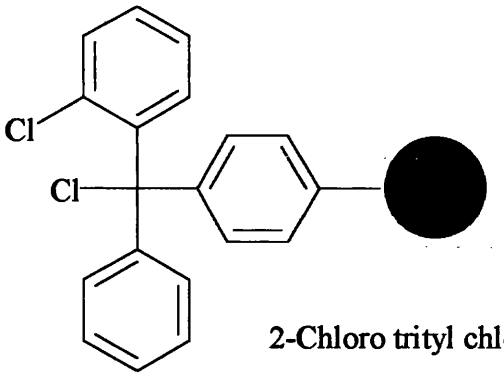
However the most commonly used resins today, such as NovaSyn KA **5**, NovaSyn TGA **6** and 2-chlorotrityl chloride **7** resins.[6,7] are resins that can be cleaved with moderate or mild acid conditions (e.g. TFA) and therefore cannot use ^{t}Boc as a protecting group since the deprotection conditions for ^{t}Boc would also cleave the peptide chain from the resin. The ideal protecting group for these resins is one that can be cleaved with very mild acidic conditions, or basic conditions. There are other protecting groups such as Bpoc **8**,[8] which is very acid sensitive or o-nitrophenyl sulfenyl group **9**,[9] which can be cleaved with thioles (Scheme 1), that meet these criteria, but the Fmoc group **11**[10] is the most commonly used protecting group.



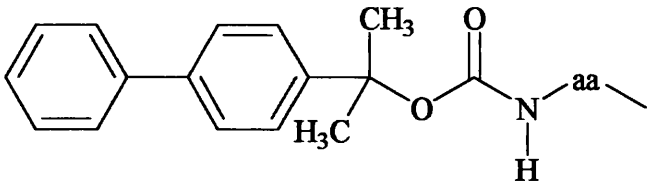
NovaSyn KA resin **5**



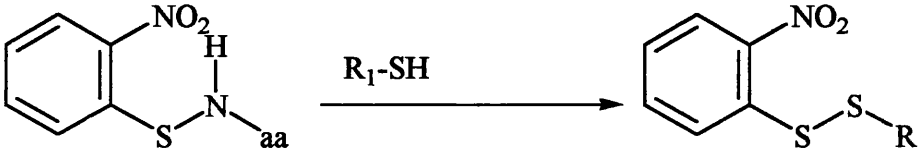
NovaSyn TGA (Tentagel acid) resin **6**



2-Chloro trityl chloride resin **7**

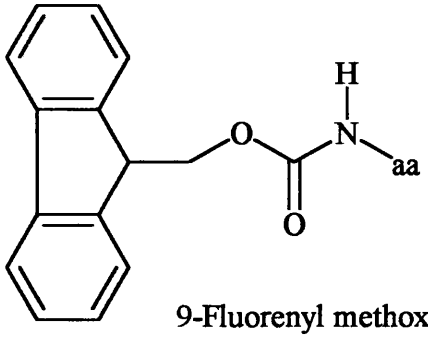


2-(4-Biphenyl) isopropyl oxycarbonyl (Bpoc) **8**



9 **10**

Scheme 1



9-Fluorenyl methoxy carbonyl (Fmoc) **11**

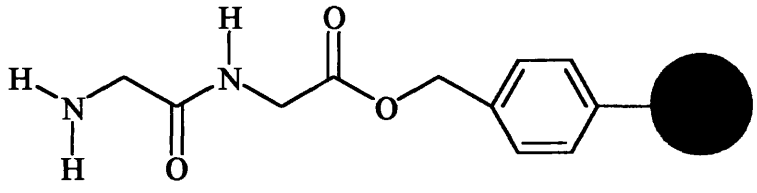
(iii) Advantages of Fmoc chemistry

There are two main advantages of using Fmoc chemistry. Firstly the loading of the resin can be easily calculated by cleaving with piperidine and using UV spectroscopy to

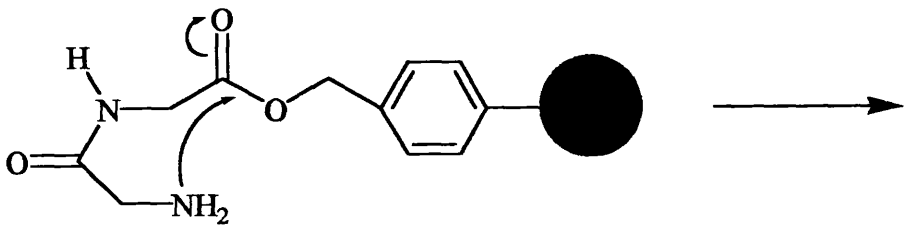
calculate the concentration of the Fmoc-piperidine adduct.[11] Secondly for a non-expert it is easier to use than ^{t}Boc chemistry. This was demonstrated when the Association of Bimolecular Research Facilities asked 40 of its members to synthesise a sixteen amino acid sequence with many difficult couplings which had the potential for side reactions.[12] Over 33 % of the crude cleavage peptides made using ^{t}Boc chemistry did not contain any of the desired peptide and 44 % of the ^{t}Boc derived peptides were unable to achieve greater than 25 % purity. For the Fmoc derived peptides over 31% of the samples had over 75% of the desired compound. However the purity of the best ^{t}Boc peptides was comparable with the results for the best Fmoc peptides. This indicates that for an "expert" user both methods give good results.

The support for the linkers varies depending on the resin which is used. In the case of NovaSyn KA resin **5** the support is silica, and of NovaSyn Tentagel resin **6** it is a polyethylene glycol chain attached to polystyrene and for 2-Chloro trityl resin **7** it is just a polystyrene chain.

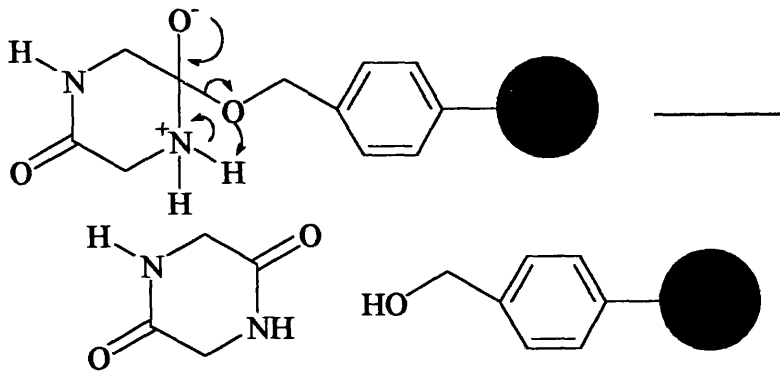
The 2-chlorotrityl chloride **7** resin is particularly useful in the synthesis of protected fragments because it can be cleaved with 5 % TFA solutions and the steric hindrance of the resin totally suppresses the formation of diketopiperazines at the dipeptide stage, which can be a problem with for example -gly-gly terminal peptides attached to Merrifield resin (scheme 2).[13] This occurs when the terminal amine in a gly -gly dipeptide attacks the ester bond in a SN2 reaction.



gly-gly-OH attached to merrifield resin **12**



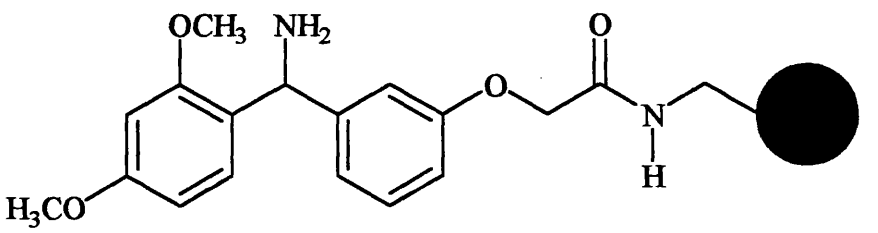
The NH_2 of the terminal glycine can attack the ester bond **13**



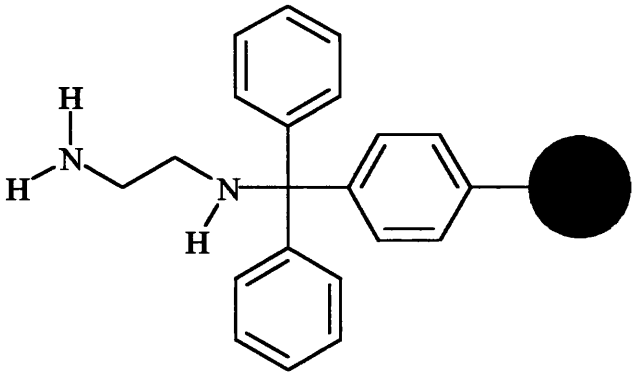
Piperazine-2,5-dione **14**

Scheme 2

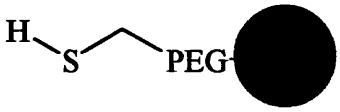
Another advantage of 2-chlorotrityl chloride is that on cleavage it produces less by-products than many other resins.[14]Although the original resins only gave peptide acids on cleavage, resins have since been developed that give peptide amides on cleavage, e.g. Tentagel rink amide (T.G.R) **15**,[15] peptide aminopropyl amines e.g. diaminoethane trityl resin **16**,[16] or thiol acids **17**.[17] The base labile HMBA resin **18** can give a variety of products depending on the method of cleavage.[18]



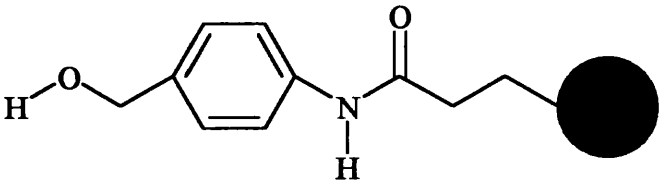
Tentagel Rink Amide TRA resin **15**



Diaminoethane trityl resin **16**

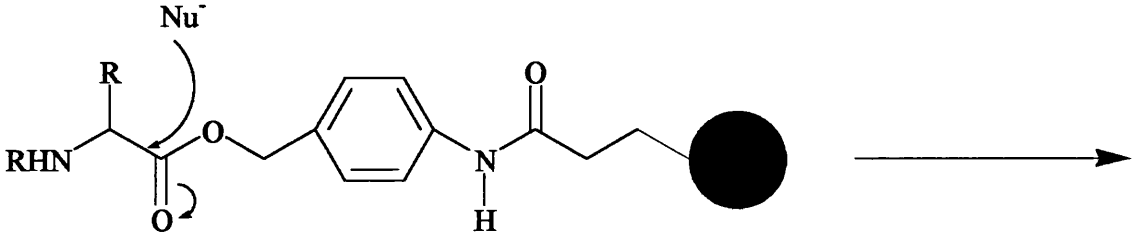


Novasyn TG Thiol resin **17**

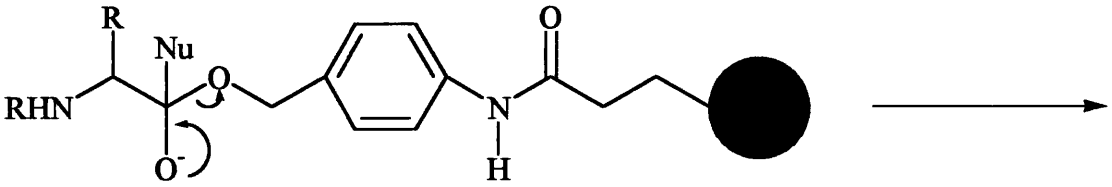


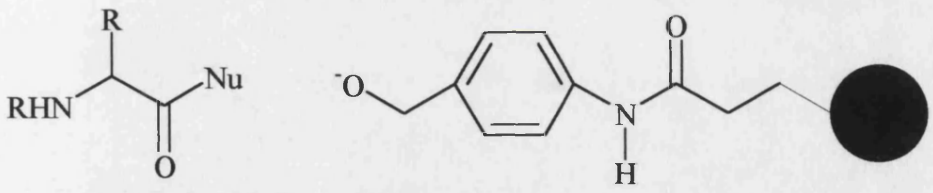
HBMA resin **18**

As Nu can equal can equal NH_3, NH_2NH_2, ^-OH, MeO^- or H^- the products can be peptide peptide amide, peptide hydrazide, peptide acid, peptide methyl ester or peptide alcohol (in the case of H the initial product is the aldehyde which is then further reduced) depending on the nucleophile (scheme 3).



peptide attached to HBMA resin **19**

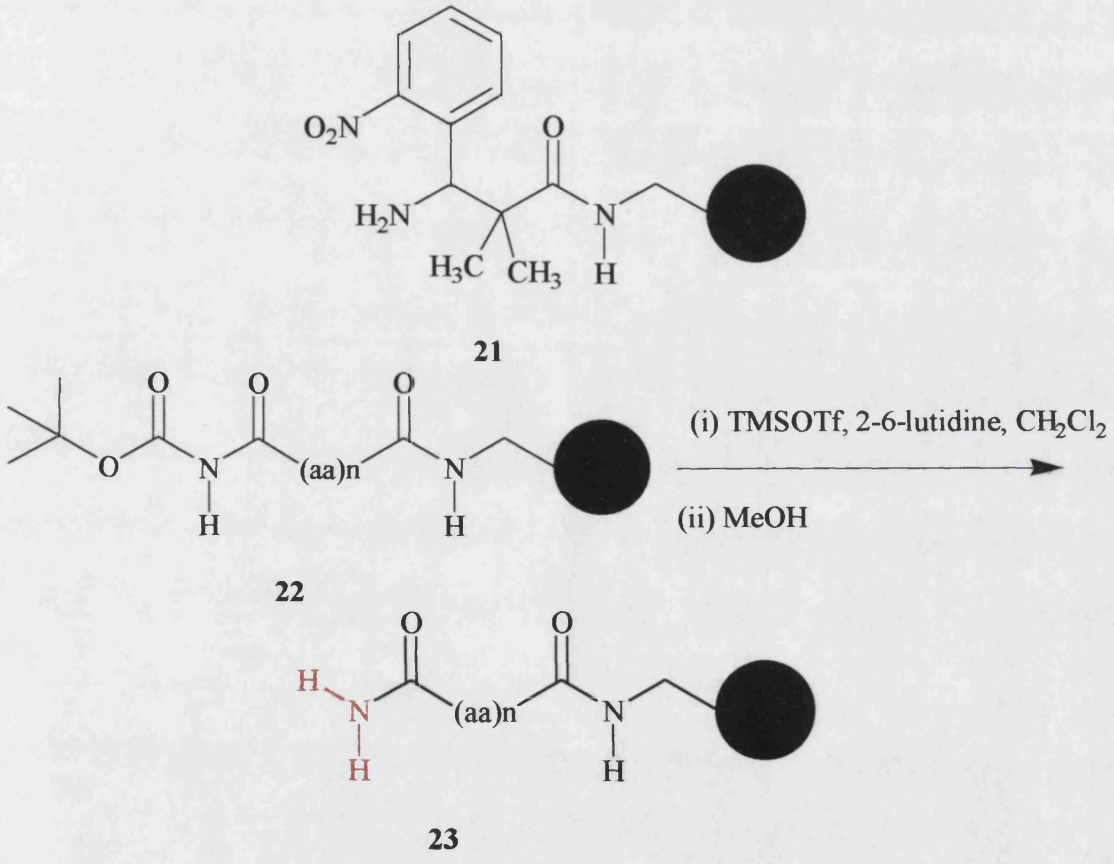




product **20**

Scheme 3

Research on linkers for resins and new methodology is still being carried out. Recent highlights have been a new photolabile linker resin **21**[19] and it is now possible to remove ^{t}Boc groups without using acid,[20] although this is not as high yielding as Fmoc chemistry (Scheme 4).[20]



Scheme 4

(iv) Disadvantages of solid phase chemistry

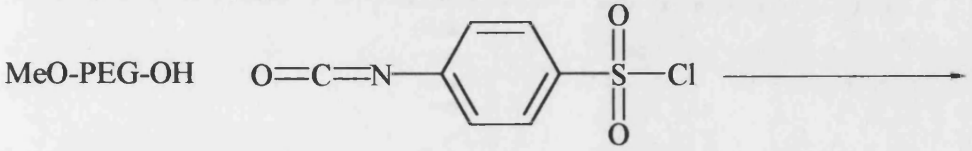
Although there are many advantages to solid phase peptide synthesis there are also disadvantages. For example although we usually do not draw the chemical structure of the solid support it is not just a "blob" that one can safely ignore because it does have an effect on the reaction. Many different polymers were investigated by Merrifield,[1] and he noted that reactions using solid phase chemistry go more slowly than those using solution phase.[1] Many resins can be damaged by mechanical stirring and although shaking is an alternative it does not mix the reagents as effectively as stirring them. The size of the beads and the amount that they swell with the solvent affects how easily the reagents can penetrate the resin. The swelling depends upon the reagent, the most common solvents used are DMF, CH_2Cl_2, THF and toluene. Solvents such as methanol tend to shrink the resin, and the process of alternating shrinking and swelling (by using methanol and CH_2Cl_2 sequentially) is often used to wash the resin.

There are other problems with solid phase synthesis. For example it is very difficult to monitor the reaction using conventional methods. Some of them are impossible e.g. tlc, others are possible but very difficult e.g. ^{13}C NMR spectrum and others are possible but difficult and do not always give useful information e.g. IR. There are colour tests one can use for the detection of primary amines such as the Kaiser test,[21] or the TBNS test,[22] or picric acid monitoring.[23] These tests indicate when an amino acid coupling has gone to completion. However for many other reactions there are not any tests to determine if a reaction has gone to completion. If a mass spectrometer can be used one can follow the reaction by cleaving a small portion of the resin and seeing in the mass spectrum if the product has been formed and/or if the starting material is still present.

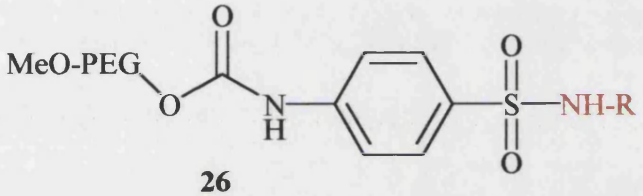
(v) Liquid / liquid phase chemistry

Liquid phase chemistry is a possible answer to the problems of solid phase chemistry as it combines many of the advantages of solid phase and solution phase chemistry. The principle

behind liquid phase chemistry is similar to solid phase chemistry in that the peptide chain or compound is attached to a support.[24,25] The difference is that the support is soluble in some solvents. The reaction is carried out in a solvent that dissolves the support and on completion of the reaction (which can be monitored by ^{1}H or ^{13}C NMR spectrum spectroscopy more easily than solid phase chemistry but less easily than solution phase) another solvent is added that causes the support and chain to crystallise from the solution. The support is then filtered, and the next reaction can be carried out or the product can be cleaved. This has been applied to the synthesis of peptide and non peptide libraries (Scheme 5).



24 **25**



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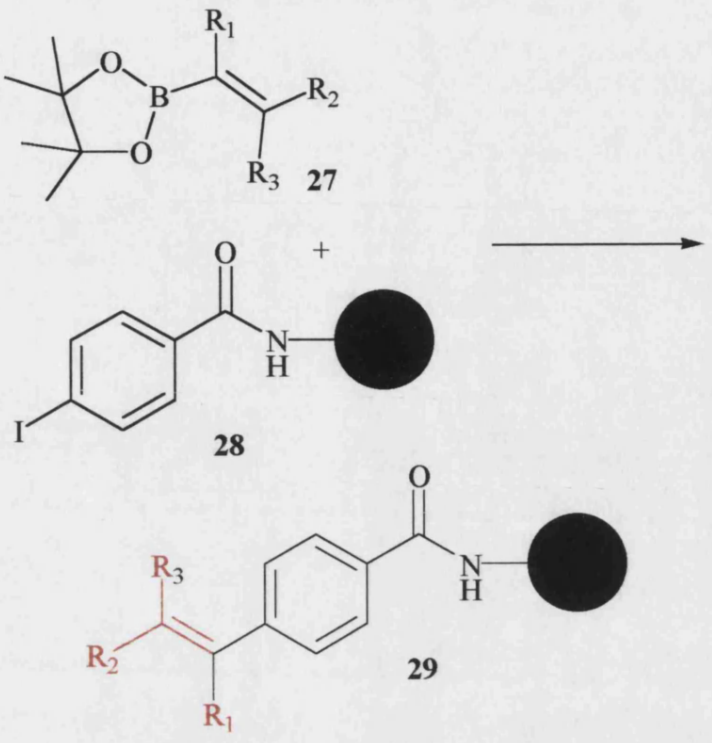
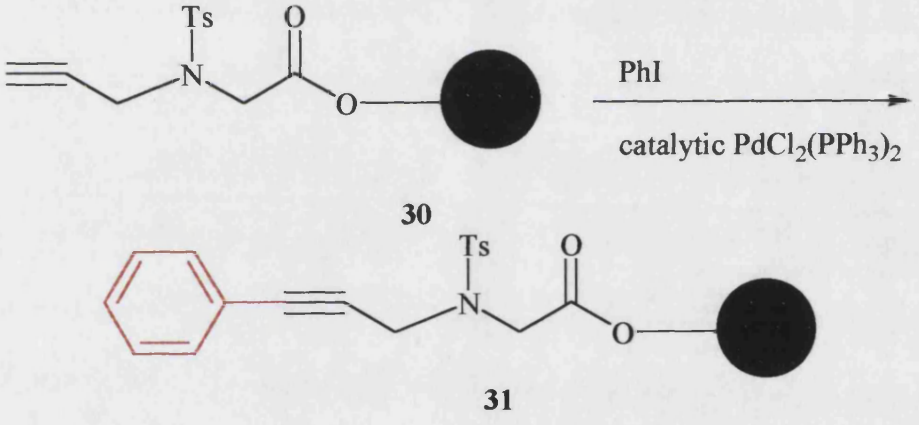
Scheme 5

(vi) Scope of solid phase chemistry

Despite the problems of solid phase chemistry, a large amount of research has been carried out on many different reactions using solid supports as well as the traditional peptide couplings attached to solid supports.[26] This is because of the recent interest in combinatorial chemistry. These reactions are not being developed with the aim of large or medium scale synthesis of chemicals, but with the aim of synthesising a large number of related but different compounds on a small scale in a short time. This enables lead compounds for drugs or pesticides to be discovered more quickly. A large number of different reactions have been recently carried out on solid supports including the Suzuki reaction (Scheme 6) and the Heck reaction (Scheme 7).[21]

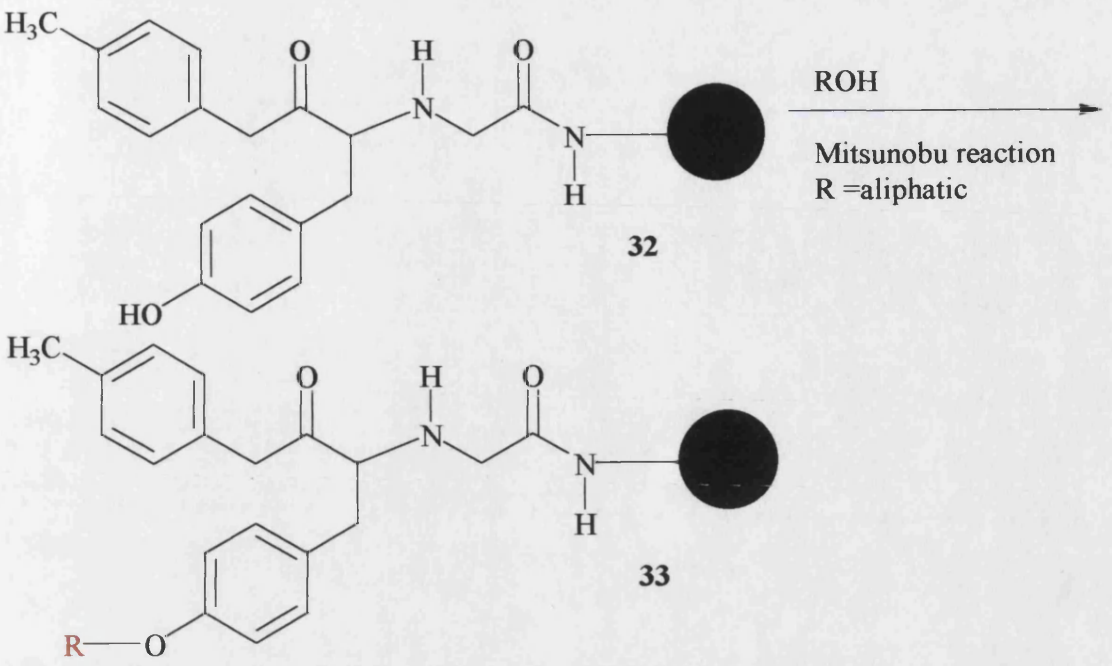


Scheme 6



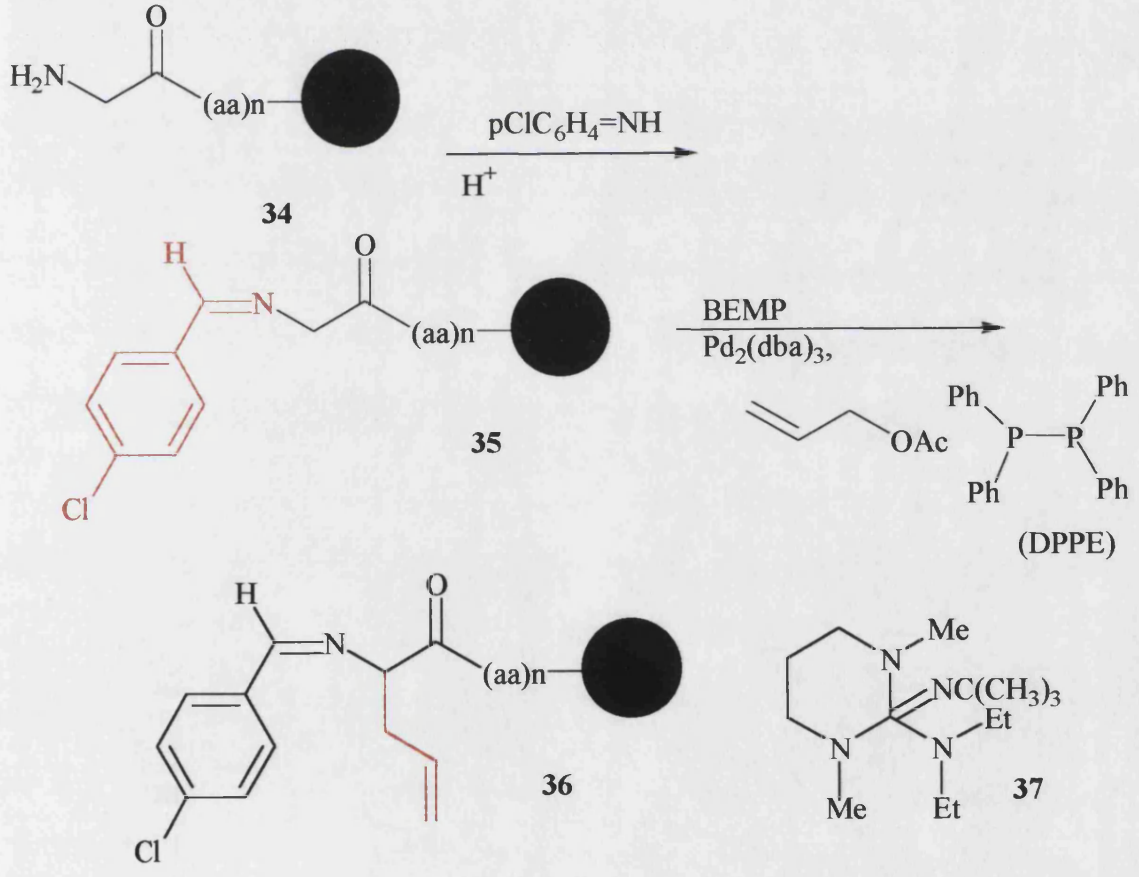
Scheme 7

Another type of reaction which can be carried out on resins is the O-alkylation of tyrosine equivalents (Scheme 8).[19]



Scheme 8

During the course of our research we allylated amino acid imines attached to 2 chloro trityl and TGR resins (Scheme 9).



Scheme 9

DPPE stands for 1,2 Bis(diphenylphosphino)ethane, BEMP stands for 2-*tert*-Butylimino-2-diethylamino-1-3-dimethylperhydro-1,3,2-diazo-phosphorine

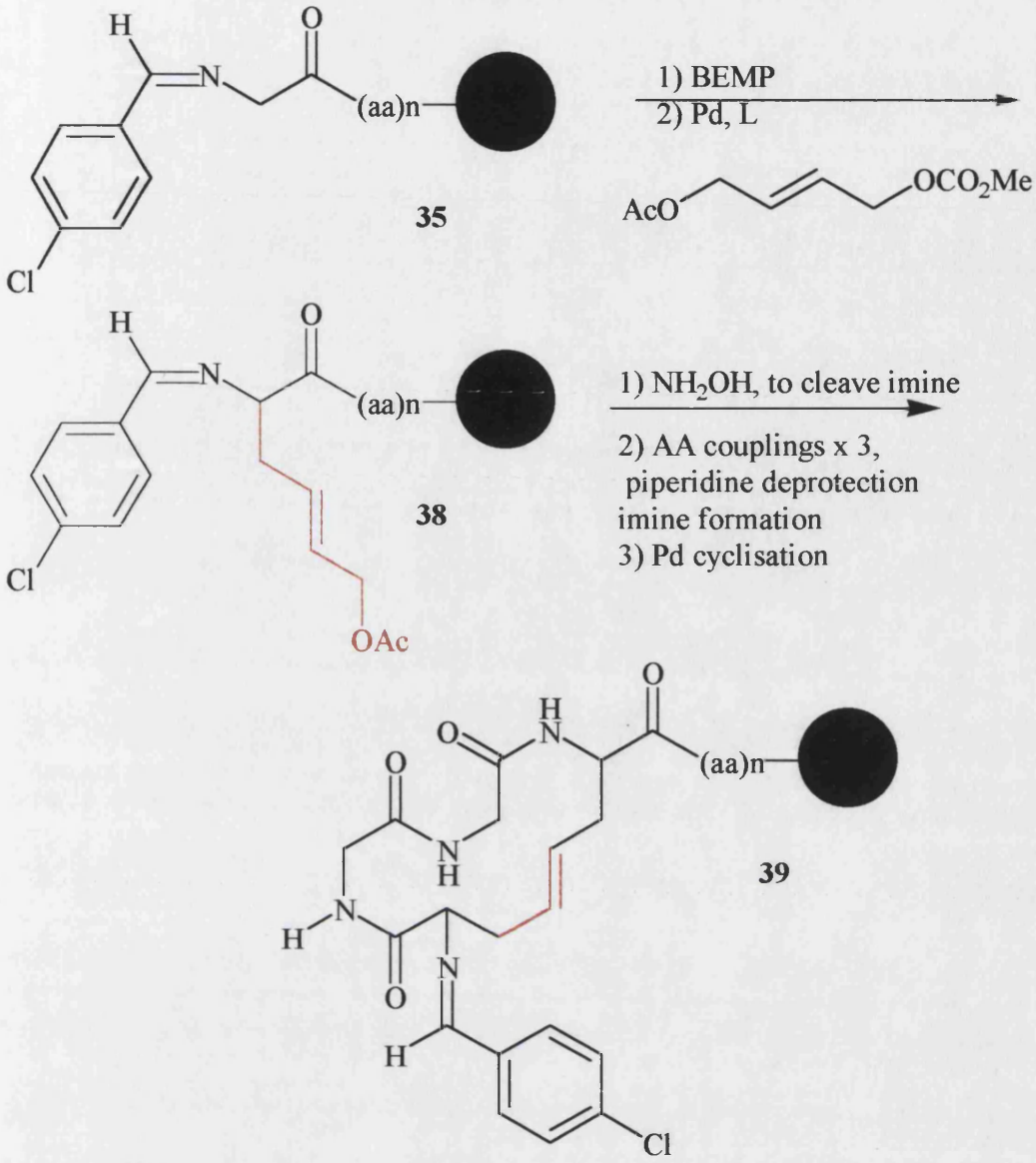
Despite the large number of reactions that have been carried out on substrates attached to solid phase chemistry there are still reactions to be carried out. One reaction which has not yet been successfully investigated is the allylation of glycine equivalents using palladium catalysis. Although there are already literature methods to synthesise peptides containing allylglycine during solid phase peptide synthesis,[27] it was considered that if the palladium catalysed allylation of amino acid equivalents could be fully developed, it might have advantages over literature methods. These are:-

i) Less toxic allyl acetates can be used instead of allyl chlorides.

ii) Enantiomerically pure ligands can be developed to control the stereochemistry.

iii) That cyclic peptides could be synthesised by using allyl systems with two different leaving groups. However a strategy for this has not yet been developed.

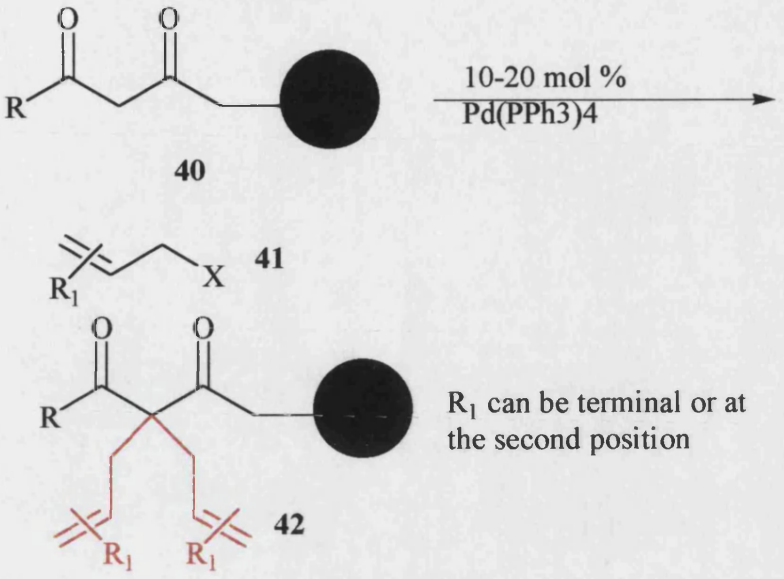
However it is known in the literature that OCO_2Me or Cl are lost preferentially instead of OAc groups, so it is possible in theory (Scheme 10).[28,29]



Scheme 10

We think that three amino acid couplings carried out on the intermediate compound would be a good attempt as with one or two amino acid residues the angle might be too strained. However, with more amino acid residues the electrophillic and nucleophillic parts of the molecule might be too far away to react.

Palladium catalysed allylic substitutions of amino acid equivalents on resin have not yet been reported in the literature, however the palladium catalysed allylation of polymer bound 1,3 dicarbonyl compounds has recently been reported (Schemes 11 or 12).[30] With more reactive allylic acetates, such as allyl or cinnamyl acetate, dialkylation was the major product. With more hindered allylic acetates or allyl chloride, mono alkylation was the main product.



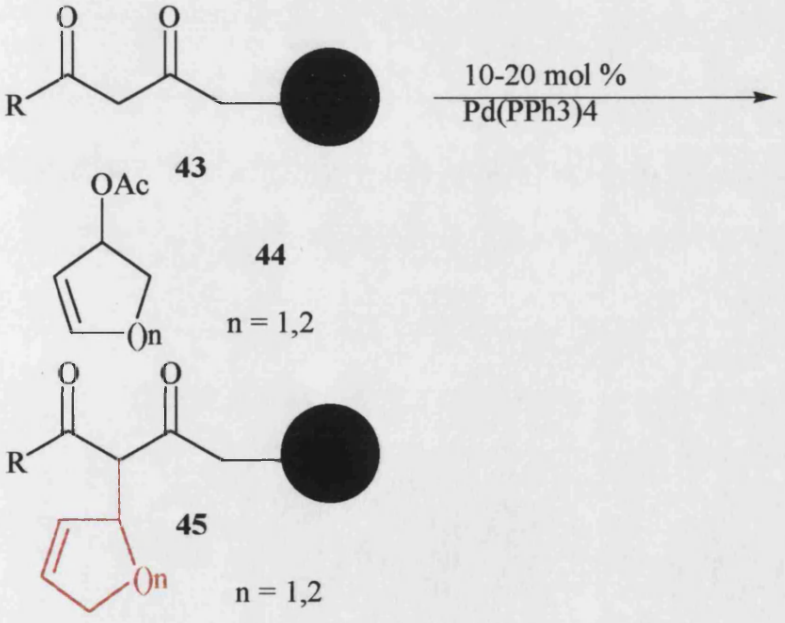
R_1 = H, Ph, 3-Furyl

2-Thienyl, 4-MeNC_6H_4

R = OMe, Me, Bn

X = OAc, O_2CO

Scheme 11



Scheme 12

Chapter 2

Palladium catalysed allylation - a brief review

Palladium catalysed reactions have been used for a number of years for a wide range of substrates both in homogenous and heterogenous catalysis. Some of the most important reactions are :-

(i) The Heck reaction

(ii) The Stille coupling

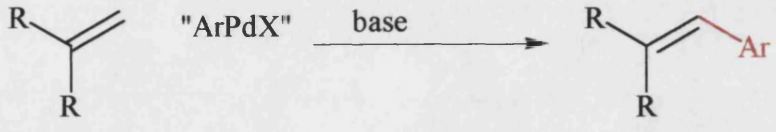
(iii) The Suzuki reaction

(iv) Wacker oxidation

(v) Allylic substituion

(i) The Heck reaction

In the Heck reaction alkenes are arylated by addition of an arylpalladium reagent generated in situ and the palladium catalyst is regenerated at the end of the reaction (scheme 13).[31] Alkyllation can also take place but only if the alkyl group does not have any hydrogens, e.g. methyl, benzyl or neopentyl groups.



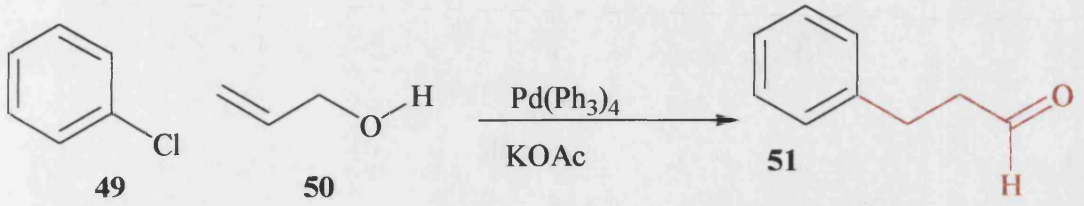
46 **47** **48**

R can be any of a variety of functional groups.

Scheme 13

A wide range of substrates can be used in the Heck reaction. The substrate can be either a simple alkene or it can contain a variety of functional groups, such as ester, ether,[32] carboxyl, phenolic or cyano groups.[33] The most reactive alkene is ethene, and with increasing substitution the reactivity is lowered. For unsymmetric alkenes substitution takes place on the

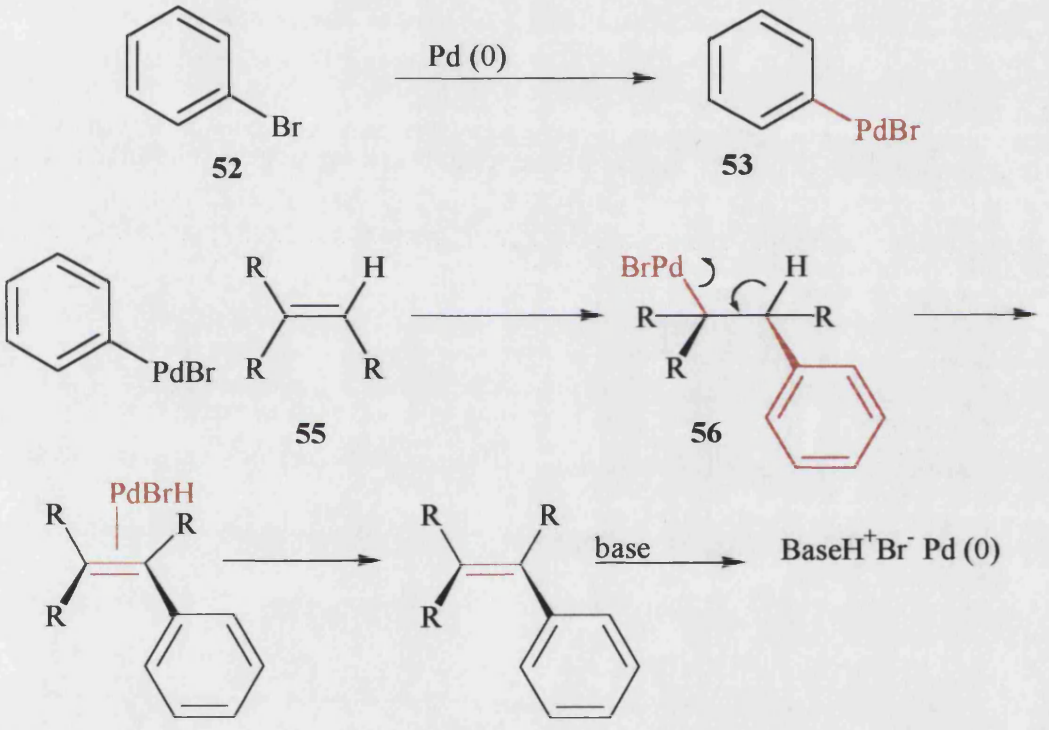
less highly substituted side of the double bond.[34] Primary and secondary allylic alcohols give aldehydes or ketones that are products of double bond migration (Scheme 14).[35]



49 50 51

Scheme 14

The reaction is via an addition-elimination mechanism (addition of ArPdX followed by elimination of HPdX) (Scheme 15).[36]

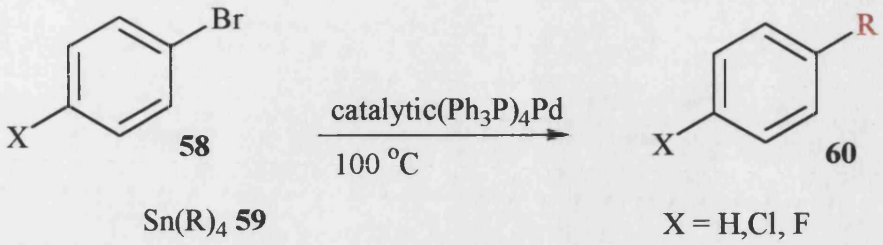


52 53 55 56

Scheme 15

(ii) The Stille coupling

Another important reaction is the Stille coupling, in which organotin reagents are coupled with a variety of organic electrophiles (Scheme 16).[37]



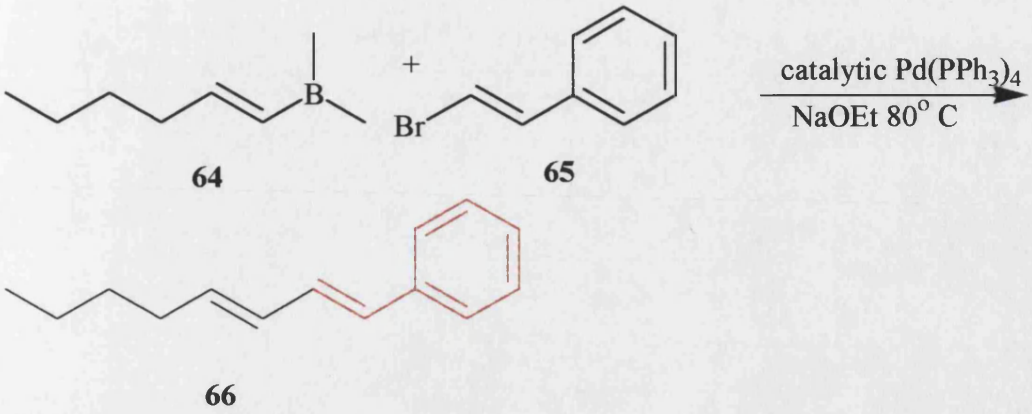
Scheme 16

Only one of the R groups is transferred and the other three R groups are wasted, which is undesirable if R is valuable. However alkyl groups are transferred more slowly than other R groups so if a non-alkyl R group is valuable R_3R^1Sn, where R = alkyl, R^1 = other, can be synthesised and R^1 will be transferred exclusively.[36] Many different classes of compounds can be synthesised by the Stille coupling, one example is the synthesis of ketones from acid chlorides (Scheme 17).[36]

Scheme 17

(iii) The Suzuki reaction

The Suzuki reaction is the coupling of alkenylboranes with alkenylbromides using a base eg NaOH or NaOEt. The products retain the configurations of both the alkenylboranes and the bromoalkenes (Scheme 18).[38]



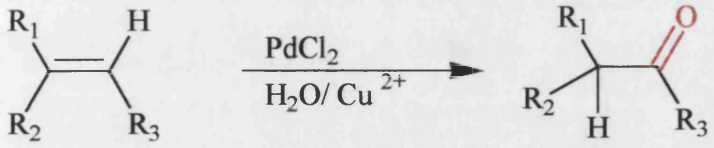
64 65

66

Scheme 18

(iv) The Wacker oxidation

In the Wacker oxidation (Scheme 19) alkenes are oxidised to carbonyl compounds. [39]



67 68

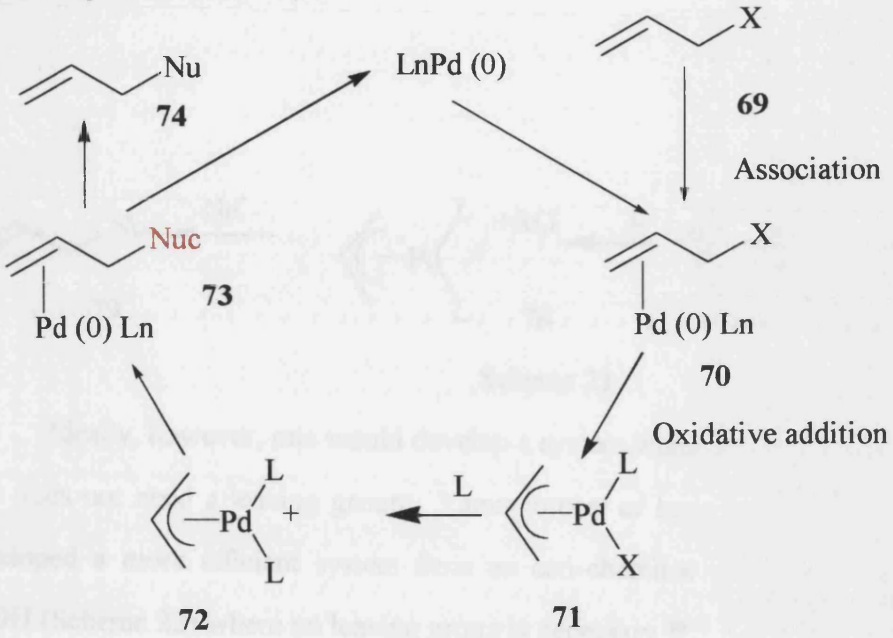
Scheme 19

The palladium chloride is reduced to Pd (0). However the Pd is reoxidised by $CuCl_2$ to Pd(II) and the Cu(I) produced is itself reoxidised to Cu(II) by atmospheric oxgyen, so that only oxygen is used up in the reaction. The reaction is used on an industrial scale to produce acetaldehyde from ethene. With other alkenes Markovnikov's rule is followed and the major product is a ketone. The generally accepted mechanism is via a π complex of Pd.[40]

(v) Allylic substitution

Another important reaction is allylic substitution which has been known for over thirty years.[41] It is believed that the mechanism of palladium catalysed allylic substitution is via the initial co-ordination of the palladium(0) to the alkene, followed by an oxidative addition process to furnish an intermediate η^3allyl complex. In the presence of a phosphine ligand, an equilibrium between a neutral and cationic complex results. The cationic complex is favoured by the use of bidentate phosphine ligands. Nucleophilic addition to the cationic complex is

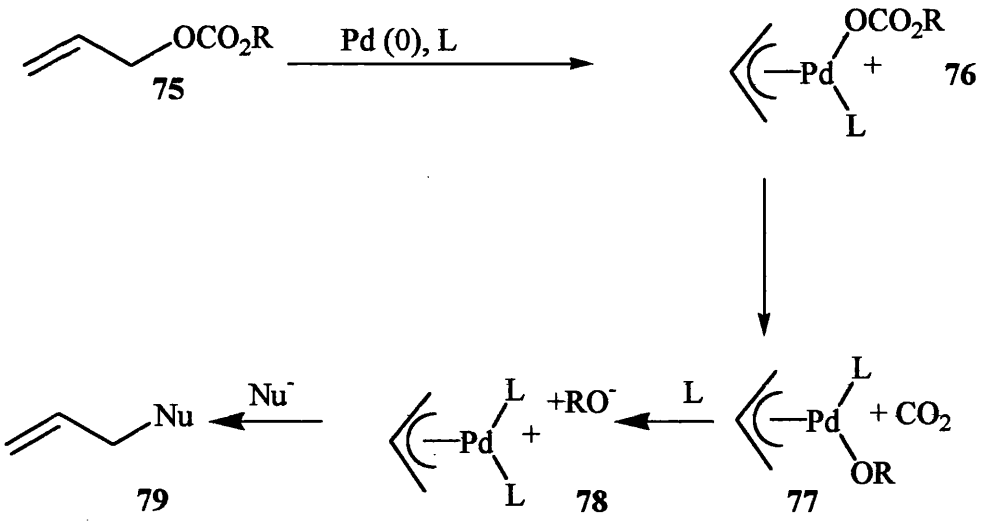
favoured, and occurs at one of the allylic termini to afford the palladium(0) complex of product. Dissociation of the palladium(0) liberates the product and regenerates the active palladium complex (Scheme 20).[42]



Scheme 20

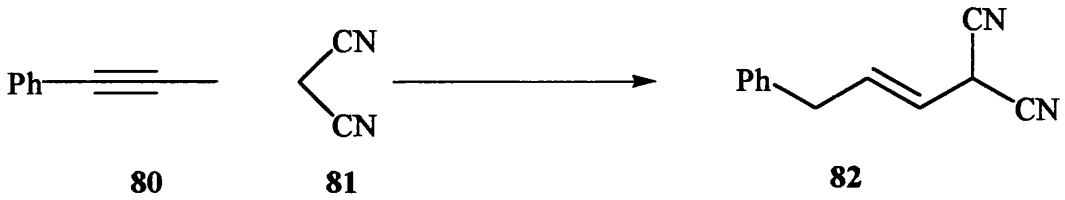
The leaving group X is usually an acetate but other groups will also function effectively, including halides,[43] sulfones,[44] carbonates,[45] carbamates, epoxides[46] and phosphates.[47]

The reaction could be more efficient chemically since at the moment the allyl compound needs a leaving group such as X which is a side product and in most cases a base has to be used to generate the nucleophile. One exception to this is with carbonates where X is $ROCO_2$ which then loses carbon dioxide to give an alkoxide (Scheme 21),[48] which can deprotonate a wide range of nucleophiles.



Scheme 21

Ideally, however, one would develop a system which not only does not need a base but also does not need a leaving group. Yamamoto *et al* have recently reported that they have developed a more efficient system from an eco-chemical point of view using alkynes and AcOH (Scheme 22) where no leaving group is necessary.[49]

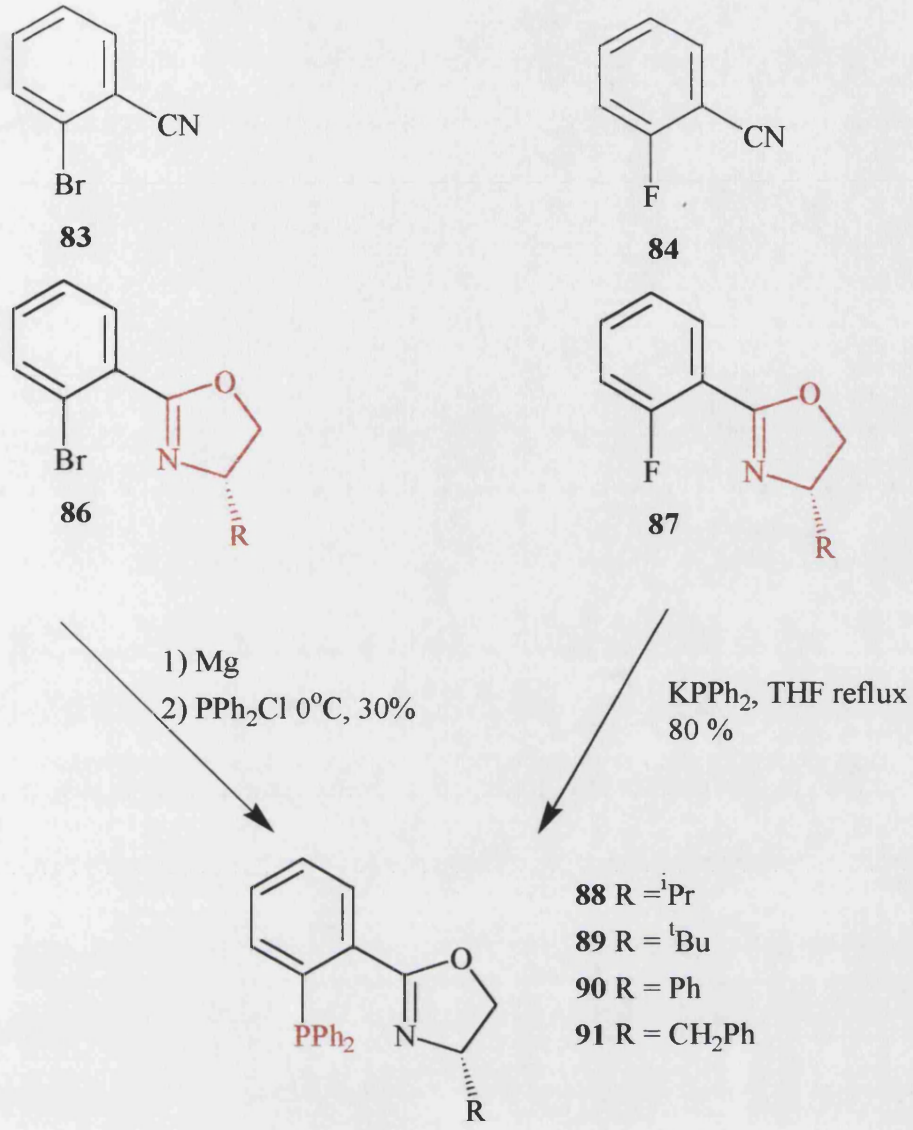


Scheme 22

This work is in the early stages and the reaction using chiral ligands has not been reported yet.[48]

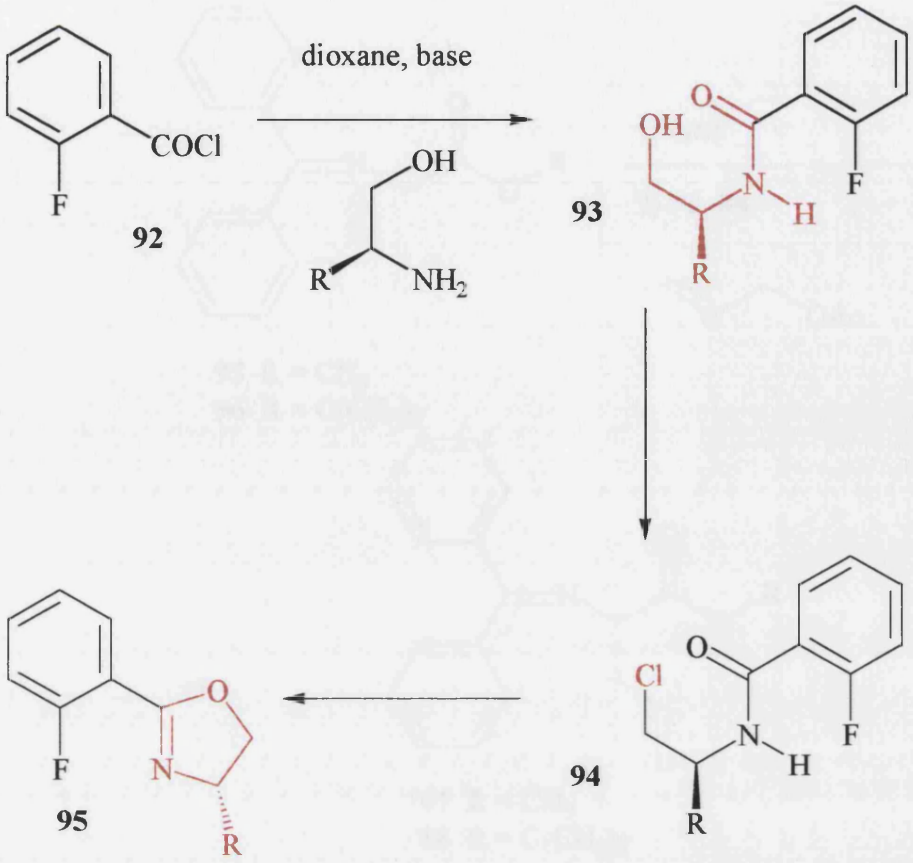
(vi) Synthesis of chiral ligands for use in Pd (0) allylation

For the more standard method of palladium allylation, a wide range of ligands has been developed including oxazolines which were simultaneously developed by Williams,[50] Helmchen,[51] and Pflatz [52] using different routes (Scheme 23).



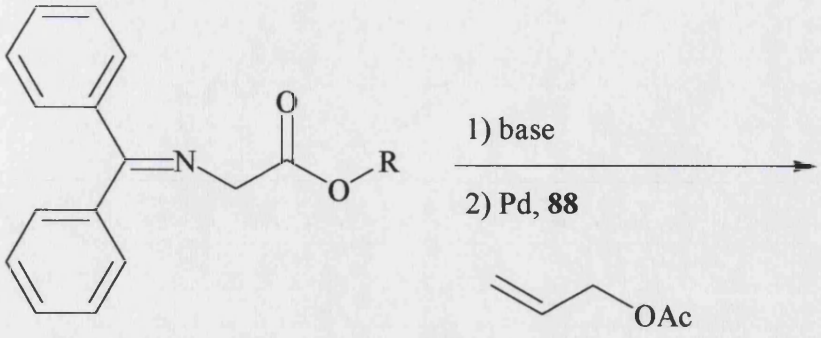
Scheme 23

Helmchen has since developed a new higher yielding route to synthesise oxazolines (Scheme 24), yielding fluorophenyl oxazolines with up to 96% overall yield.[53]

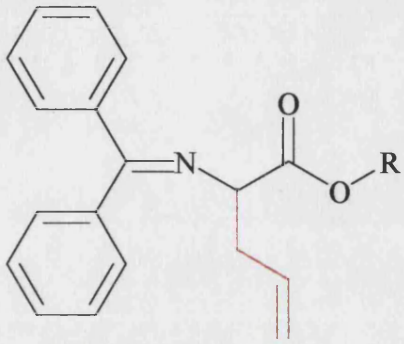


Scheme 24

These ligands provide excellent levels of stereocontrol for a wide range of electrophiles and nucleophiles with up to 98% ee[49,50,51] However for some reactions, such as the allylation of glycine equivalents in solution phase chemistry, the stereocontrol has been disappointing, with poor stereocontrol yielding 17 % ee using ligand **88** (Scheme 25).[54]



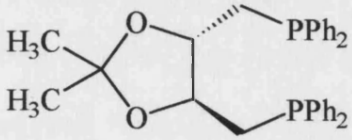
95 R = CH_3
96 R = $C(CH_3)_3$



97 R = CH_3
98 R = $C(CH_3)_3$

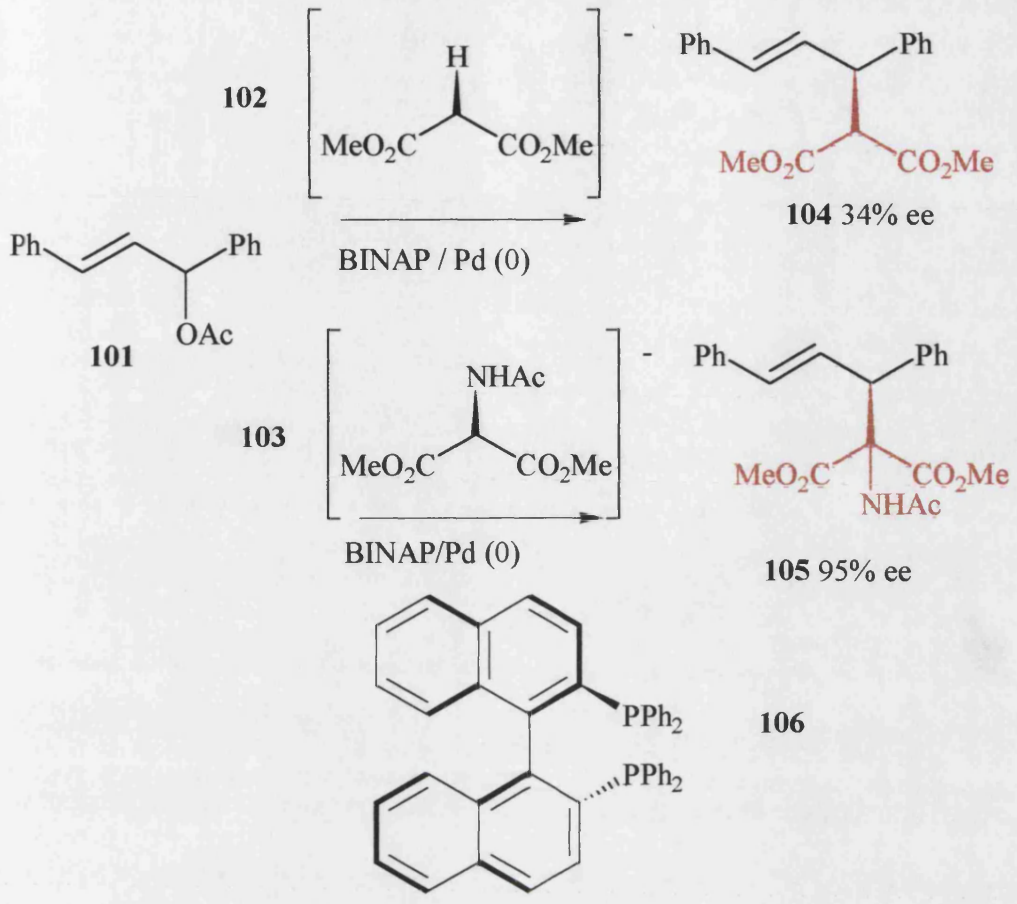
Scheme 25

The highest stereocontrol for this reaction is 70 % ee, achieved by Genet *et al*, using (+) DIOP**99**.[55]



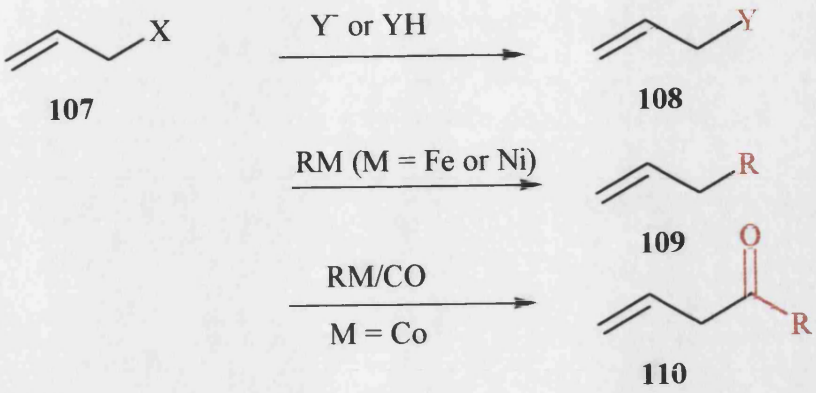
99 (+) DIOP

It is perhaps surprising that DIOP has the best stereocontrol for this reaction as it is one of the oldest ligands used in palladium chemistry, having been utilized by Trost *et al* in 1973.[56] Another ligand that has been used for some time is BINAP **100**. BINAP also shows the effect of nucleophile on stereocontrol, as the reaction of the allylic acetate **101** with malonic acid dimethyl ester **102** gives an ee of 34% but with 2-Acetylamino-malonic acid dimethyl ester **103** an ee of 95% is obtained (Scheme 26).[57]



Scheme 26

A wide range of nucleophiles have been used in the reaction. The most commonly employed are the 'soft' stabilised carbanions such as dimethyl malonate, but under appropriate conditions nitrogen based nucleophiles,[58] sulfur nucleophiles,[59] oxygen nucleophiles,[60] phosphorus nucleophiles,[61] silicon nucleophiles,[62] vinyl boranes,[63] hydrides (borohydrides / aluminohydrides[64] and formates[65]), tetraphenylborate,[66] organometallics (dialkylzincs,[67] Grignards,[68] organoaluminium reagents,[69] organozirconium reagents,[70] organotin reagents[71]) have all been employed.[72] In the presence of carbon monoxide and suitable nucleophiles carbonylation reactions have also been achieved, as in (Scheme 27).[73]



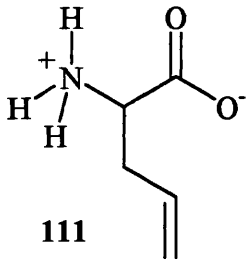
107 **108** **109** **110**

Scheme 27

Chapter 3

Allylation of glycine equivalents during solid phase synthesis - model studies and their application to solid phase synthesis

Allyl glycine **111** is a known enzyme inhibitor,[74] so it was decided to investigate the use of palladium chemistry to synthesize peptides incorporating allyl glycine and similar compounds such as cinnamyl glycine. Eventually the methodology could be used to synthesise cyclic peptides see above.

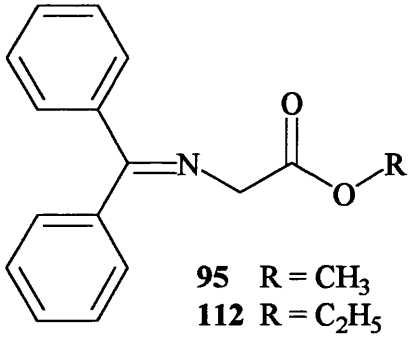


111

(i) Model studies using glycine ester imines

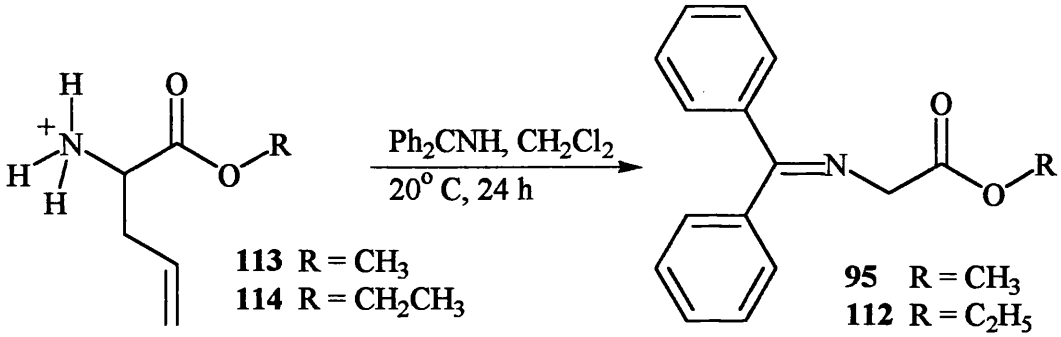
(ii) Synthesis of imines

It was decided to begin the research by allylating activated glycine esters, using *N*-(diphenyl methylene)-gly-OEt **112** and the known compound *N*-(diphenyl methylene)-gly-OMe **95**[75] as models.



95 R = CH_3
112 R = C_2H_5

These were synthesised according to the method of O'Donnell *et al*,[76] where the amino acid ester hydrochloride salt was stirred with benzophenone imine in DCM. The solvent was removed *in vacuo* and the crude material dissolved in ethyl acetate and washed sequentially with water and $NaHCO_3$ solution. The ethyl acetate was then removed *in vacuo* to afford *N*-(diphenyl methylene)-gly-OEt as a colourless solid **112** in 80% yield and *N*-(diphenyl methylene)-gly-OMe **95** as an oil in 54% yield (Scheme 28).

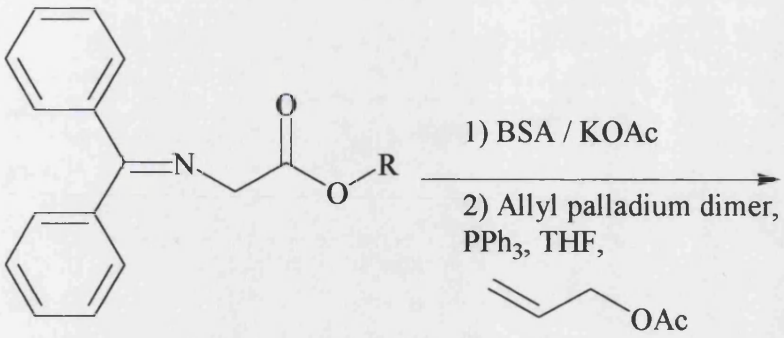


Scheme 28

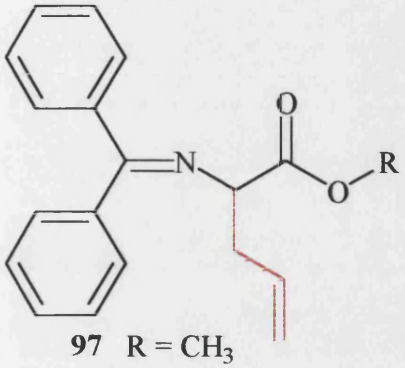
The percentage yield for the *N*-(diphenyl methylene)-gly-OEt **112** was greater than that for the *N*-(diphenyl methylene)-gly-OMe **95** although this was probably due more to the reaction being undertaken on a bigger scale than for any other reason. The ^1H NMR spectrum for *N*-(diphenyl methylene)-gly-OMe **95** had the CH_2 signal at 4.22 ppm, and in the ^{13}C NMR spectrum the signal was at 55.5 ppm. The ^1H NMR spectrum for *N*-(diphenyl methylene)-gly-OEt **112** had both CH_2 signals at 4.22 ppm, but the signals in the ^{13}C NMR spectrum were different with 55.7 ppm for OCH_2 and 60.0 for CH_2.

(iii) Allylation of amino acid esters

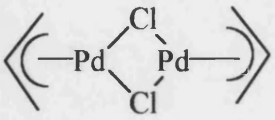
Treatment of the imino esters **95** and **112** with base, allyl palladium chloride dimer, allyl acetate and ligand afforded the allylated products *N*-(diphenyl methylene)- allylgly-OMe **97** and *N*-(diphenyl methylene)-allylgly-OEt **115** by means of the palladium catalysed allylation reaction (Scheme 29).



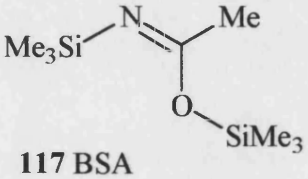
95 or **96** R = $C(CH_3)_3$



97 R = CH_3
115 R = C_2H_5



allyl palladium dimer
116



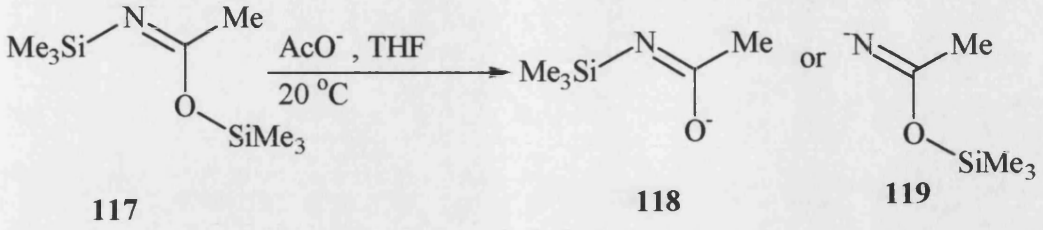
117 BSA
N,O-(Bistrimethyl silyl) acetamide

Scheme 29

The reaction went well (particularly using imine **112**) although it was important to ensure that moisture was excluded from the apparatus.

The formation of the allylated products was confirmed by inspection of the ^{1}H NMR spectrum which showed that the CH_2 singlet (4.22 for both compounds) had been replaced with a CH multiplet (4.11 for *N*-(diphenyl methylene)-allylgly-OMe **97**, (4.16 for the *N*-(diphenyl methylene)-allylgly-OEt **113** and the typical allyl CH multiplet (5.6). The $CH{=}CH_2$ signals occurred at 5.0 ppm **97** and 5.0-5.1 ppm **113** respectively. In the ^{13}C NMR spectrum the C signal next to the imine changed from a CH_2 (61.4 for *N*-(diphenyl methylene)-allylgly-OMe, 60 for the *N*-(diphenyl methylene)-allylgly-OEt) to give a CH signal (65.2 for the *N*-(diphenyl methylene)-allylgly-OMe, 65.3 for *N*-(diphenyl methylene)-allylgly-OEt). The $CH{=}CH_2$ signals were observed at 117.4 ppm **97** and 117.5 ppm **113** respectively. In the IR of *N*-(diphenyl methylene)-allylgly-OMe **97** the typical C=O peak was observed at 1739 cm^{-1} and C=N at 1660 cm^{-1}.

BSA/KOAc is a very convenient moderate base since the BSA is activated by the AcO^- which removes the TMS group from BSA. As the reaction produces more AcO^- more base is produced (Scheme 30).



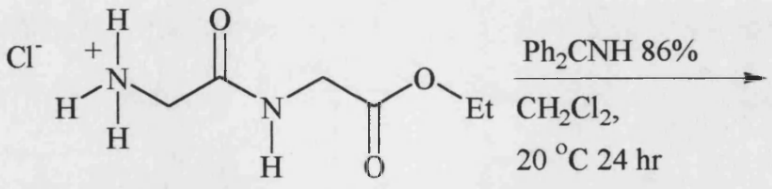
117 **118** **119**

Scheme 30

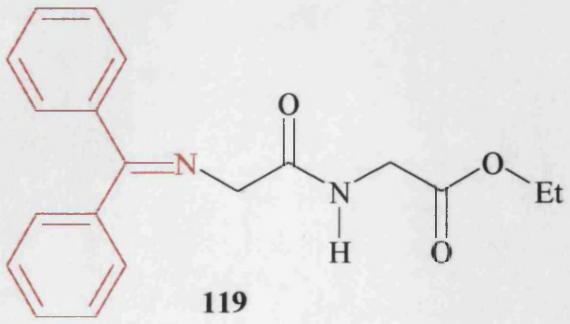
(iv) glycine glycine ethyl ester imines model studies for solid phase synthesis

(v) Synthesis of an activated and protected glycine equivalent

Following the success with amino acids, the allylation of -gly-gly-OEt**118** was attempted. Treatment of this with benzophenone imine afforded *N*-(diphenyl methylene)-gly-gly-OEt (120) which both activated the adjacent CH_2 and protected the NH_2. This synthesis was achieved by use of the same synthetic pathway as for **95** and **101** (Scheme 31).



118



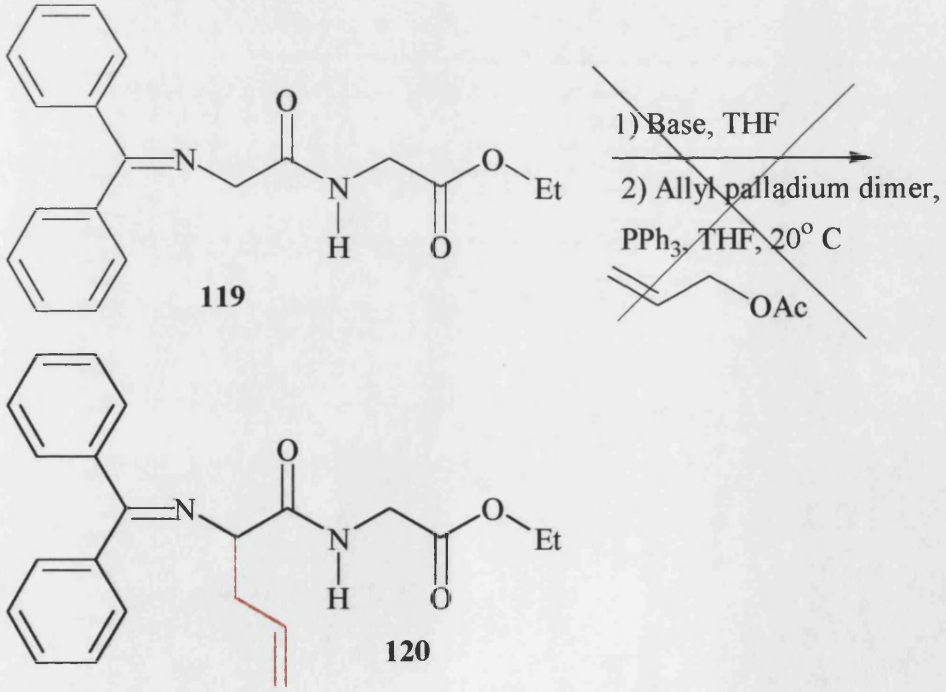
119

Scheme 31

The reaction went well giving a white solid (86 %) following an aqueous work up. The formation of *N*-(diphenyl methylene)-gly-gly-OEt was confirmed by looking at the accurate mass (M^+ 325.1553, $C_{19}H_{25}N_2O_3$ requires 325.1552) and the ^1H NMR spectrum which had a CH_2 singlet at 4.4 ppm that was assigned as the methylene group adjacent to the imine moiety. In addition there was a difference in solubility between the product and the starting material (the starting material is aqueous soluble but organic insoluble and the product is the reverse) which showed that the hydrophilic nature of the dipeptide had been changed. The hydrophilic nature of the dipeptide is because of the hydrogen bonds which are formed between the NH_2 moiety and water. Since this is no longer the case, it must be as a result of the NH_2 having reacted.

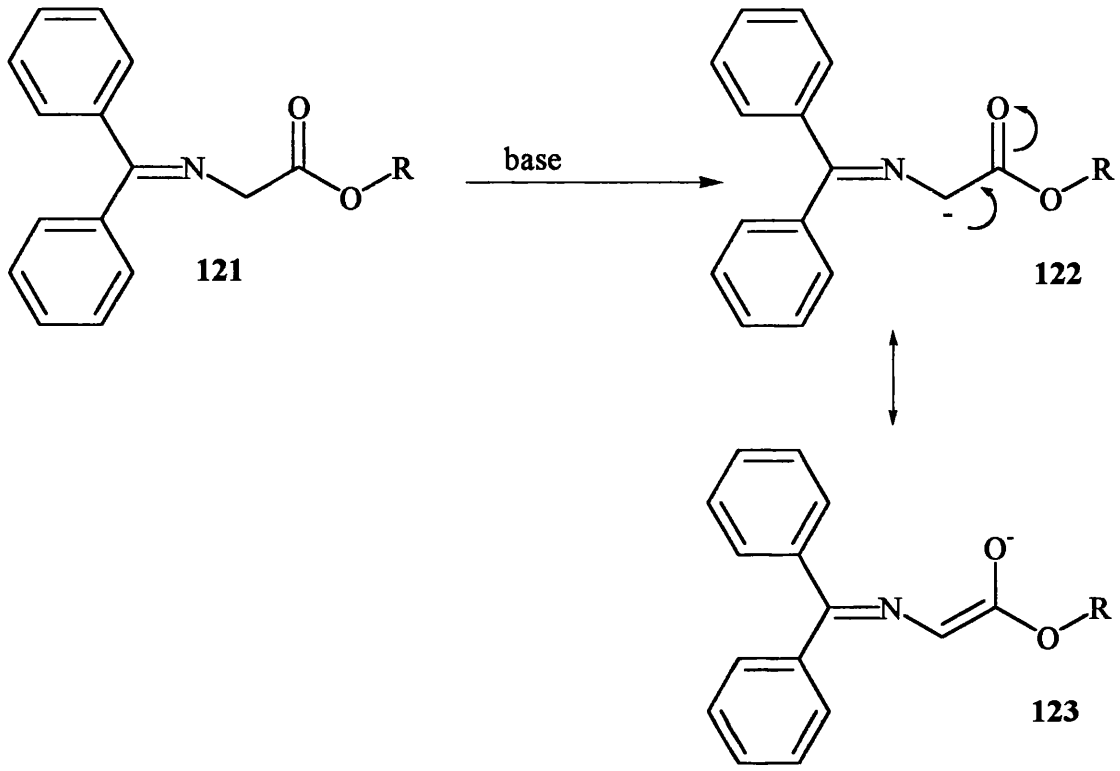
(vi) Attempts to allylate the activated glycine equivalent

Although the allylation was attempted with a wide variety of bases there was no reaction with any of them. The starting material did not react and there was no sign of allylation (Scheme 32).



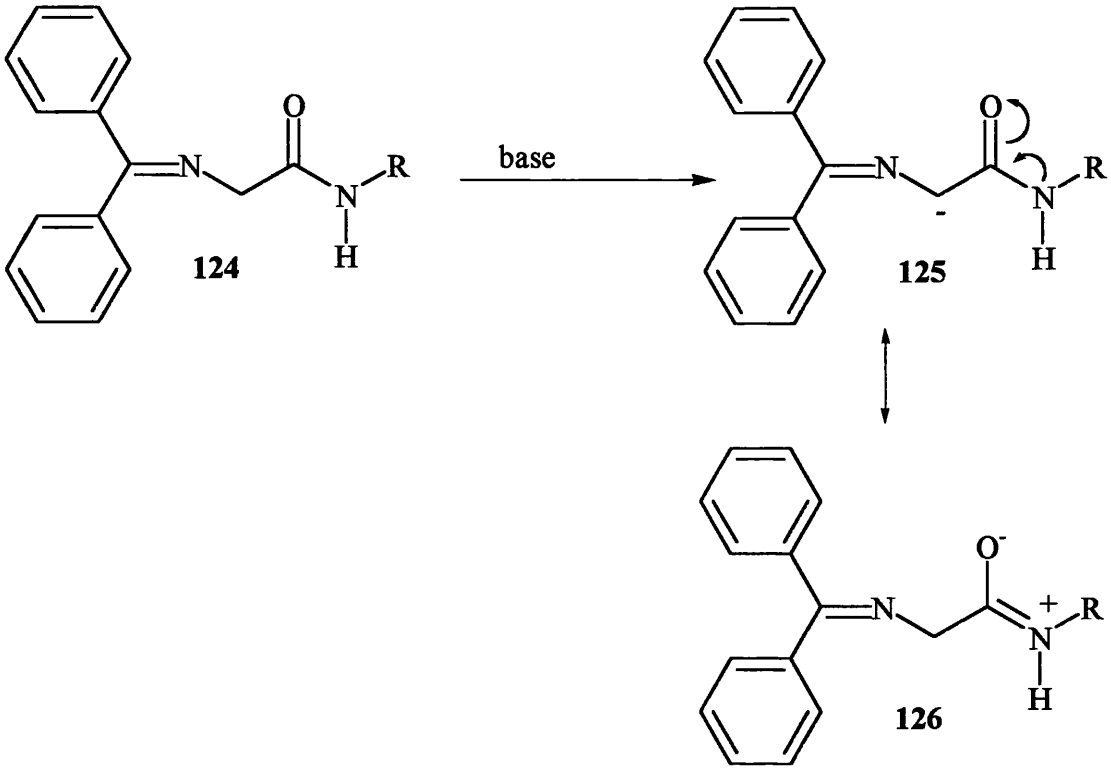
Scheme 32

The failure to allylate *N*-(diphenyl methylene)-gly-gly-OEt **119** was a problem, although not an entirely unexpected one, since it was thought that the replacement of an ester with an amide would make the formation of the anion more difficult (Schemes 33 and 34).



Scheme 33

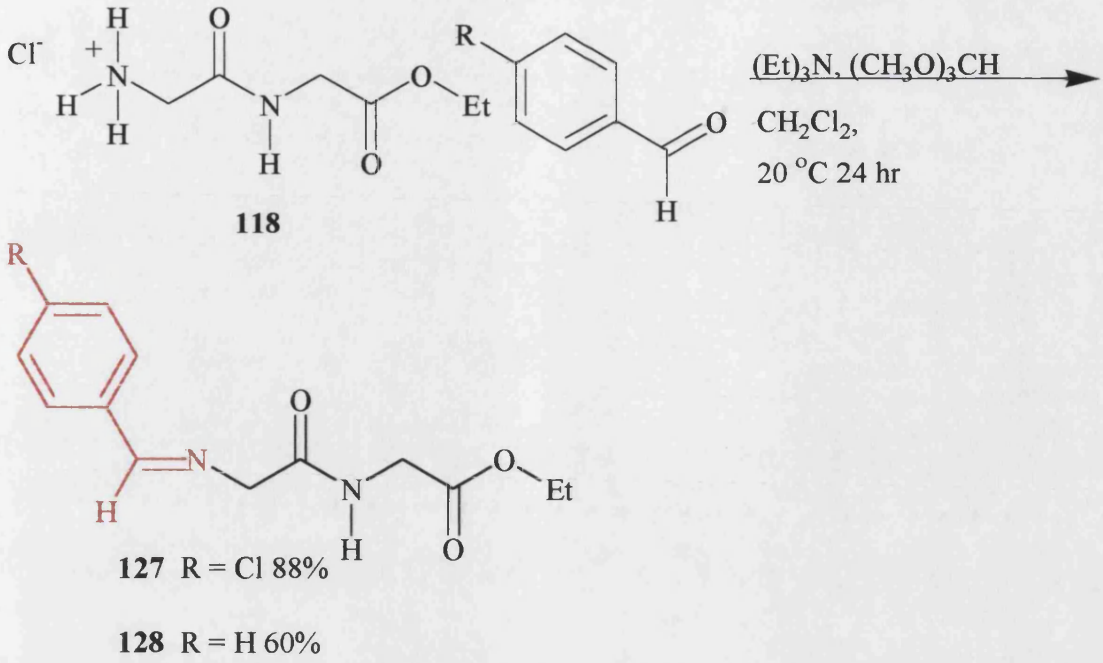
An enolate derived from an amide is harder to form since the normal resonance is compromised because of the donation of electron density into the carbonyl group by the lone pair of electrons on the nitrogen.



Scheme 34

(vii) Synthesis of other glycine glycine ethyl ester imines

The chlorobenzaldehyde **127** and benzaldehyde **128** derived imines (*N*-(*p*-chloro phenyl methylene and *N*-(phenyl methylene)-gly-gly-OEt were then synthesised after the method of Stork (Scheme 35) from gly-gly-OEt and chlorobenzaldehyde or benzaldehyde.[77]



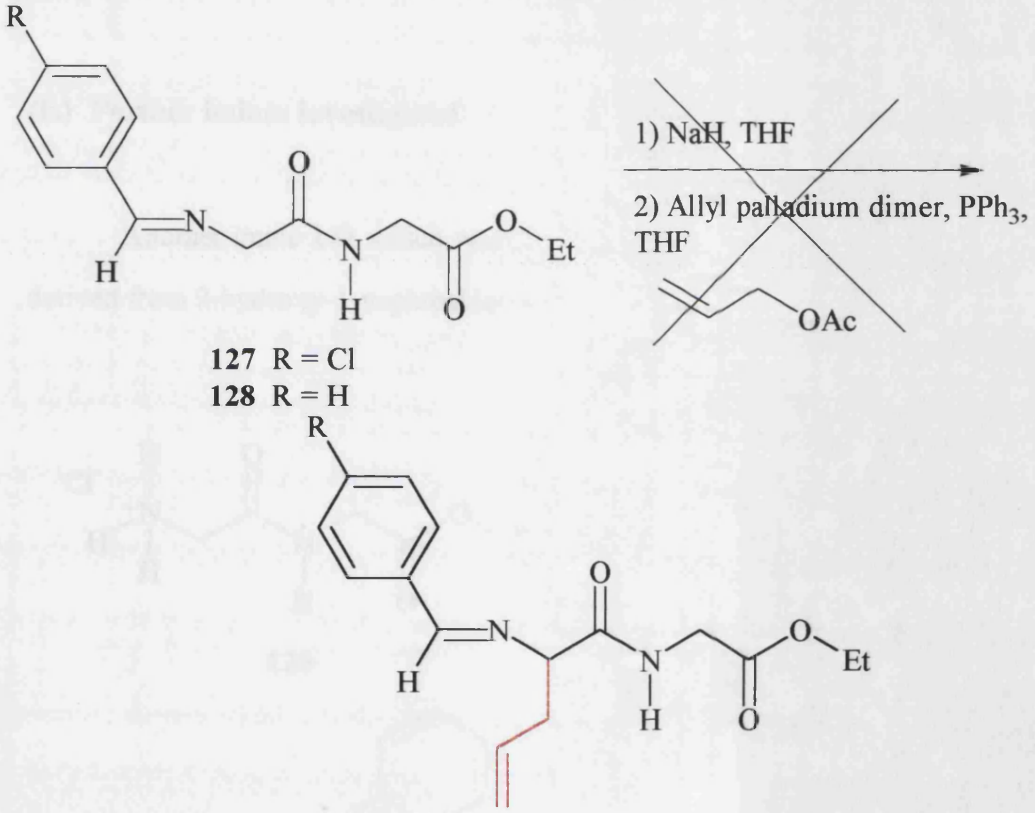
Scheme 35

It was hoped that the above compounds would prove to be more reactive, as there is less steric hindrance and, according to the literature,[78] protons adjacent to a chlorobenzaldehyde derived imine are more acidic (3.3 pK_a units) than those derived from benzophenone imine and therefore should form the anion more easily. Both reactions were carried out in a similar manner - the amino acid hydrochloride and the aldehyde were stirred together in CH_2Cl_2 with a base (triethylamine) and a dehydrating agent (trimethyl orthoformate). The reaction was followed by monitoring the disappearance of the amine with ninhydrin. The reactions were successful with a good yield (88 %) for ethyl *N*-(*p*-chloro phenyl methylene)-gly-gly-OEt **127** which was a white crystal. The crystal structure was analysed by x-ray crystallography. The yield for *N*-(phenyl methylene)-gly-gly-OEt **128** was moderate (60 %) and the product was an oil. Neither compound was stable on either silica or alumina TLC sheets. The identity of the product was confirmed by analysis of the ^1H NMR spectrum which showed the characteristic methylene singlet adjacent to the imine moiety at 4.31ppm for both compounds. The corresponding peak was slightly different in the ^{13}C NMR spectrum which showed 61.4 ppm for *N*-(*p*-chloro phenyl methylene)-gly-gly-OEt **127** and 62.4 ppm for **128**. The accurate masses were similar to the expected values, for *N*-(*p*-chloro phenyl methylene)-gly-gly-OEt **127** ($M+1^+$, 283.0844, $C_{13}H_{15}N_2O_3Cl$ requires M^+

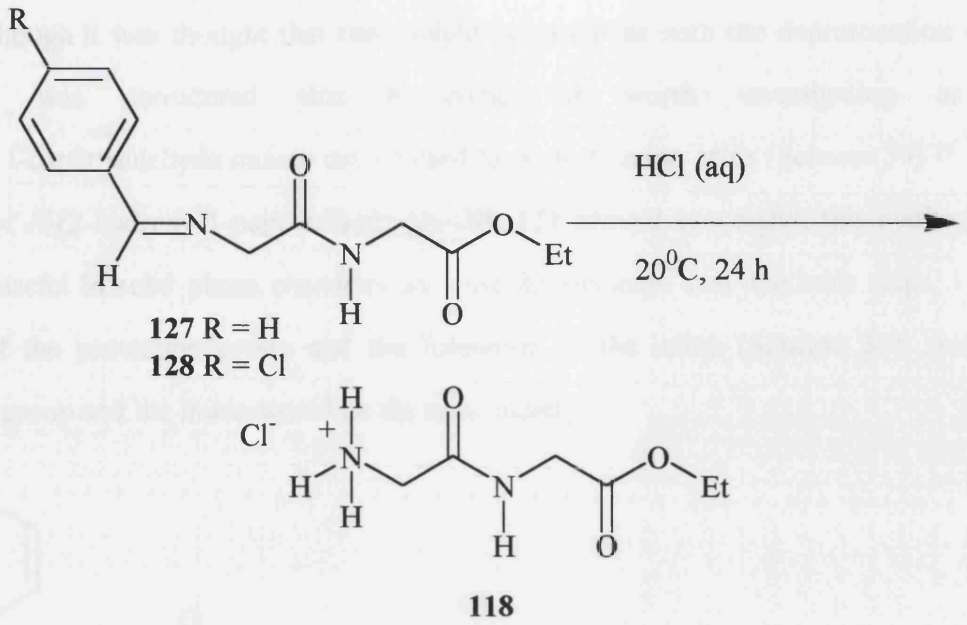
283.0849) and for *N*-(phenyl methylene)-gly-gly-OEt **128** (M^+, 249.1240, $C_{13}H_{16}N_2O_3$ requires M^+249.1239).

(viii) Attempted allylation of these compounds

As before the allylation of these compounds was tried with various different bases, but no product was formed (Scheme 36). It proved very difficult to follow these reactions as the compounds decomposed on silica which made it hard to see if the compound was reacting. This also made it more difficult to purify the final product. Purification was achieved by acid hydrolysis of the esters to recover unreacted gly-gly-OEt in water (Scheme 37).



Scheme 36

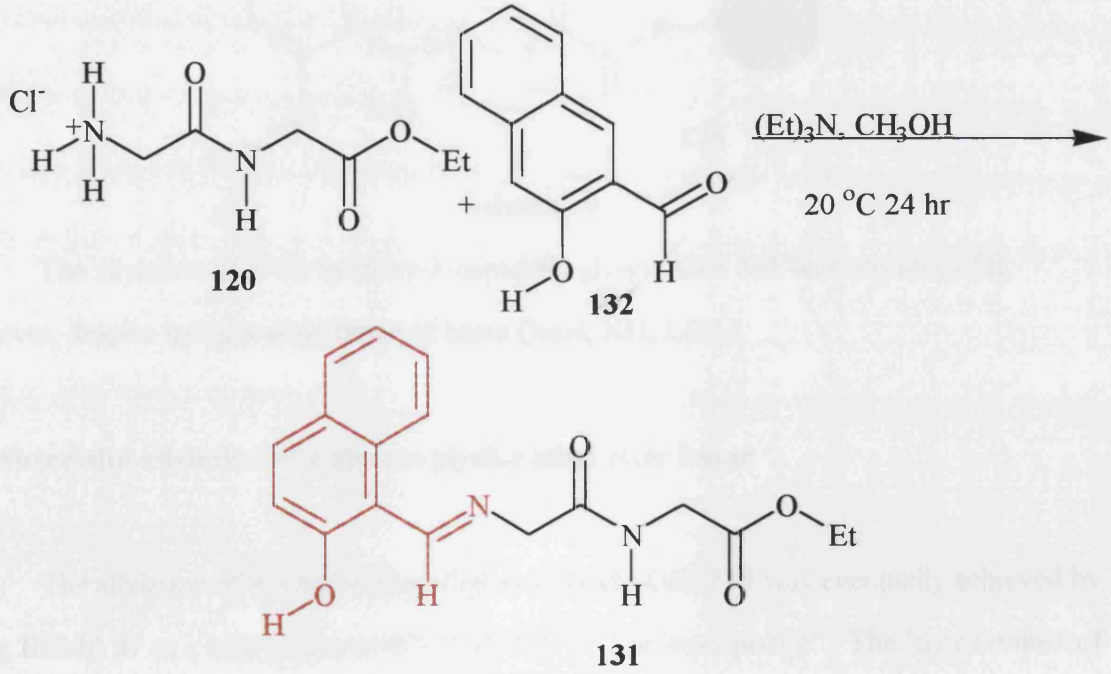


118

Scheme 37

(ix) Further imines investigated

Another imine **131** which was *N*-(2-hydroxy-1-napathal)-gly-gly-OEt investigated was derived from 2-hydroxy-1-naphthaldehyde **132** (Scheme 38).

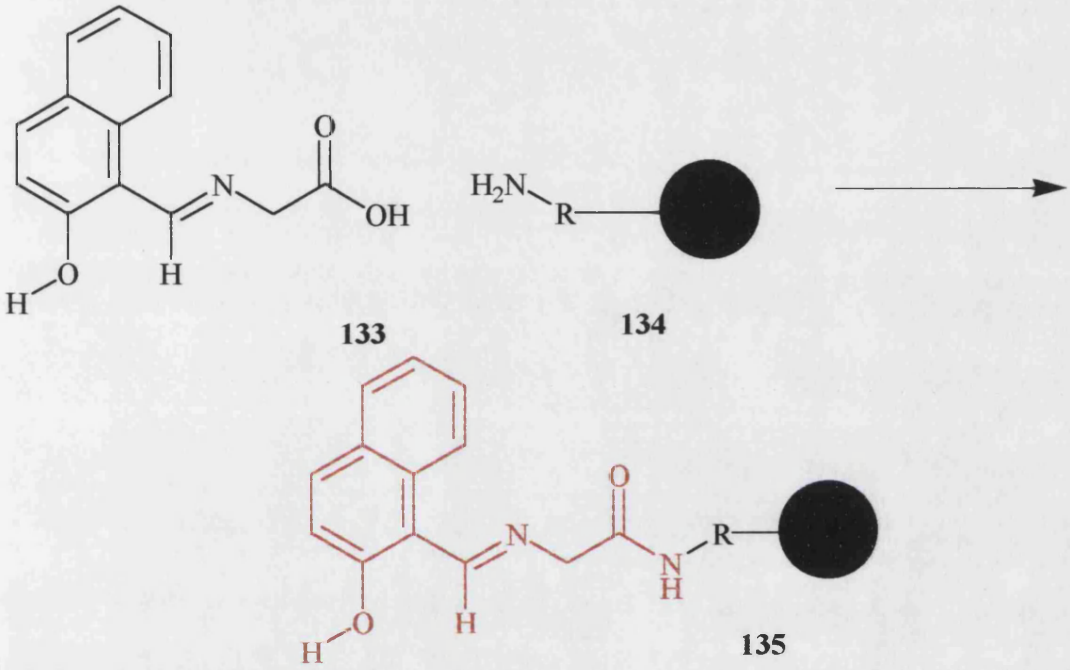


120 **132**

131

Scheme 38

Although it was thought that there might be problems with the deprotonation of the imine, it was considered that it could be worth investigating as the 2-hydroxy-1-naphthaldehyde moiety can be used to protect amino acids (Scheme 39).[79] If the allylation of *N*-(2-hydroxy-1-napathal)-gly-gly-OEt **131** proved successful, this methodology would be useful in solid phase chemistry as it would eliminate two synthesis steps, i.e. the removal of the protecting group and the formation of the imine (Scheme 39), since the protecting group and the imine would be the same moiety.



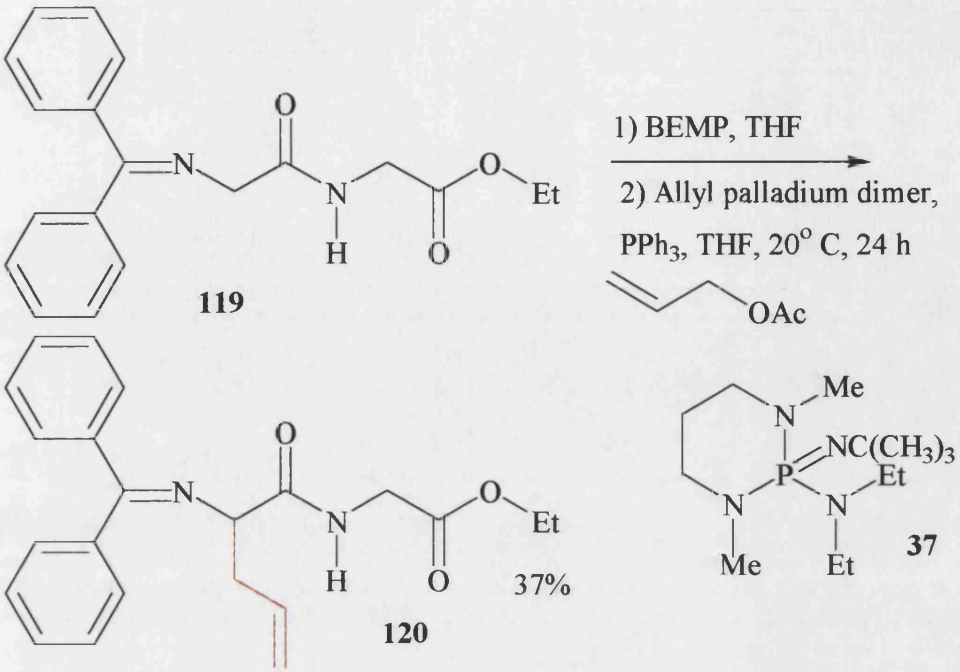
Scheme 39

The allylation of *N*-(2-hydroxy-1-napathal)-gly-gly-OEt **131** was unsuccessful, however, despite trying a wide range of bases (NaH, KH, LDA).

(x) Successful allylation of a glycine glycine ethyl ester imine

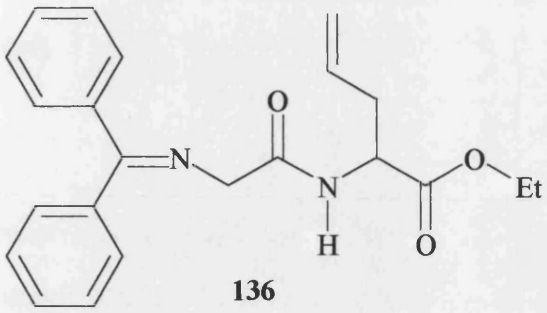
The allylation of *N*-(diphenyl methylene)-gly-gly-OEt **119** was eventually achieved by using BEMP **37** as a base (Scheme 40).[80] BEMP is a "proton sponge". The large number of N atoms it has gives it a very high basicity - over 1200 times higher than DBU, and in addition

t is much more sterically hindered, which causes it to be a very strong, non-nucleophilic base.[79]

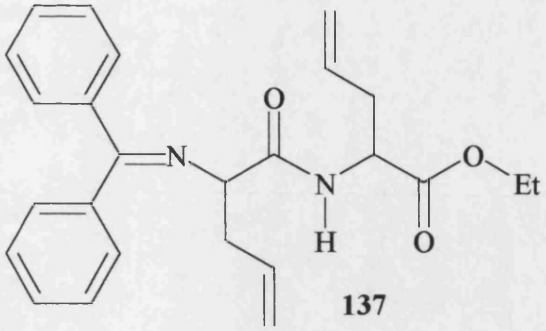


Scheme 40

The reaction was reasonably successful giving the product **120** *N*-(diphenyl methylene)-allyl-gly-gly-OEt was characterised by ^{1}H & ^{13}C NMR spectrum spectroscopy. The singlet at 4 ppm in the ^{1}H NMR spectrum **119** disappeared and the CH_2 in the DEPT ^{13}C NMR spectrum at 61.4 ppm was replaced by a CH signal at 65.5 ppm. In contrast the signal corresponding to the CH_2CO_2Et was barely changed in the NMR spectrum spectra and in the DEPT was still a CH_2 from which it was concluded that only the terminal glycine had been allylated. There were no products which showed signs of allylation at the glycine attached to the ethyl ester, *N*-(diphenyl methylene)-gly-allylgly-OEt **136** or signs of diallylation *N*-(diphenyl methylene)-allylgly-allylgly-OEt **137**.



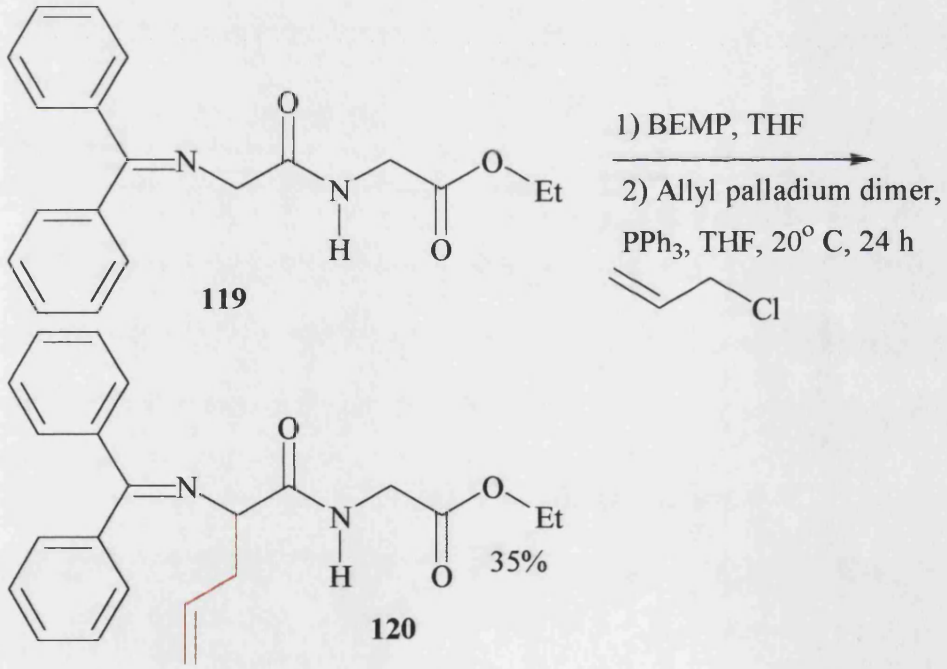
136



137

An accurate mass of **120** was not obtained, but in subsequent work a similar compound *N*-(diphenyl methylene) gly-L-ala-OEt **235** was allylated to give *N*-(diphenyl methylene)-allylgly-L-ala-OEt **238** and an accurate mass was obtained for this compound.

We also performed the reaction using the allyl chloride as the electrophile (Scheme 41). However as the yield (35%) was comparable to the reaction using the allyl acetate, it was decided to concentrate on using the less toxic and more readily available acetate instead of the chloride.



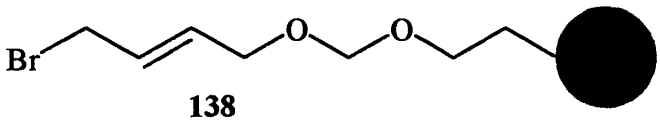
119

120

Scheme 41

(xi) Application of the reaction to solid phase synthesis

The next area of the research was to apply this work to solid phase synthesis. This was not a trivial task as expertise had to be developed to (a) load the resins, (b) form the imine, (c) carry out the palladium chemistry and (d) cleave the product. The main problems were a) formation of the imine bond on the resin bound amino acid/peptide chain and b) the reproducibility of the palladium catalysed allylation. Both of these were affected by the nature of the resin solid support which is a very important factor. Although in the following diagrams the resin is drawn as a "blob" it is not something which can be ignored. It affects the reaction as different resins swell to differing extents in different solvents. The more a resin swells the easier it is for the reaction mixture to penetrate the resin matrix and therefore the better and more reproducibly the reaction proceeds. Therefore the resin has a significant effect on the reaction. In addition the linker affects the stability of the resin to different reagents. For example resins such as **138** which are cleaved using Pd (0) and PPh_3 would be unsuitable for our work. Another important factor is the solvent because every solvent or solvent mixture swells a resin differently.

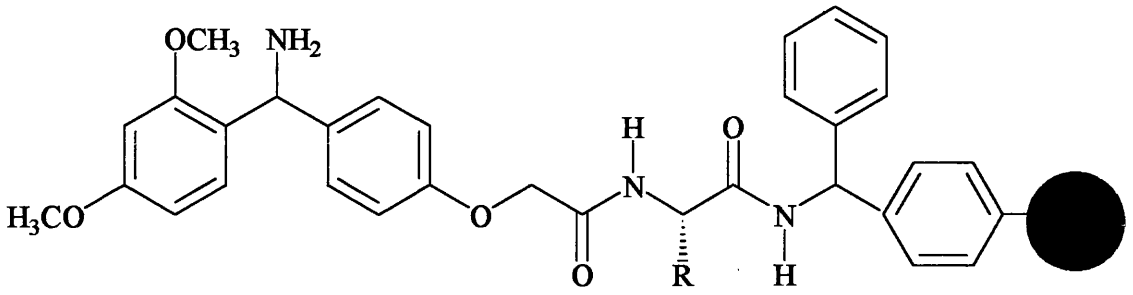


138

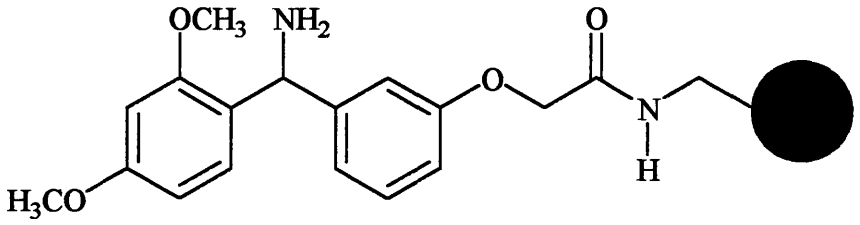
While it was easy to work out which resins would be unsuitable it was more difficult to work out which were the most suitable. The requirement was that we had to find out which resin would have the least adverse affect on the chemistry. Although the reaction was not as reliable as we had hoped when we started the project, it had never been achieved before and it is therefore a useful addition to the range of palladium catalysed reactions.

(xii) Loading of the resin

The first resins tried were Rink Amide MBHA **139** and Tentagel Rink Amide **12**.

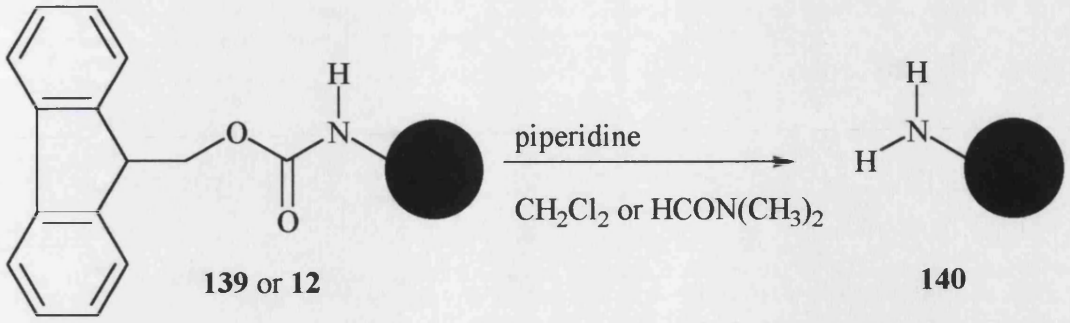


139

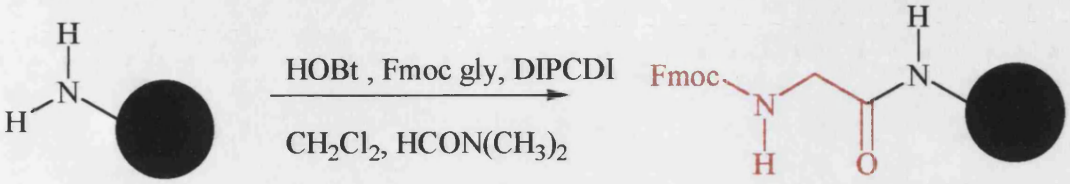


12

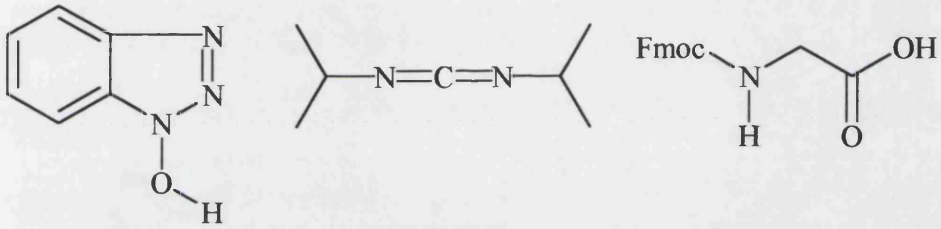
The reason for trying these two resins initially was the ease of introducing the amino acid on to the resin and of calculating the loading of the resin. Since both resins have NH_2 linker groups (sometimes they were supplied in the Fmoc protected form, so that the resin had to be deprotected with piperidine prior to use) the coupling of the amino acid was repeated until all the NH_2 groups had reacted. Then coupling of the amino acid was carried out using HOBt **142** and DIPCDI **143** as coupling agents (Scheme 42).



139 or **12** **140**



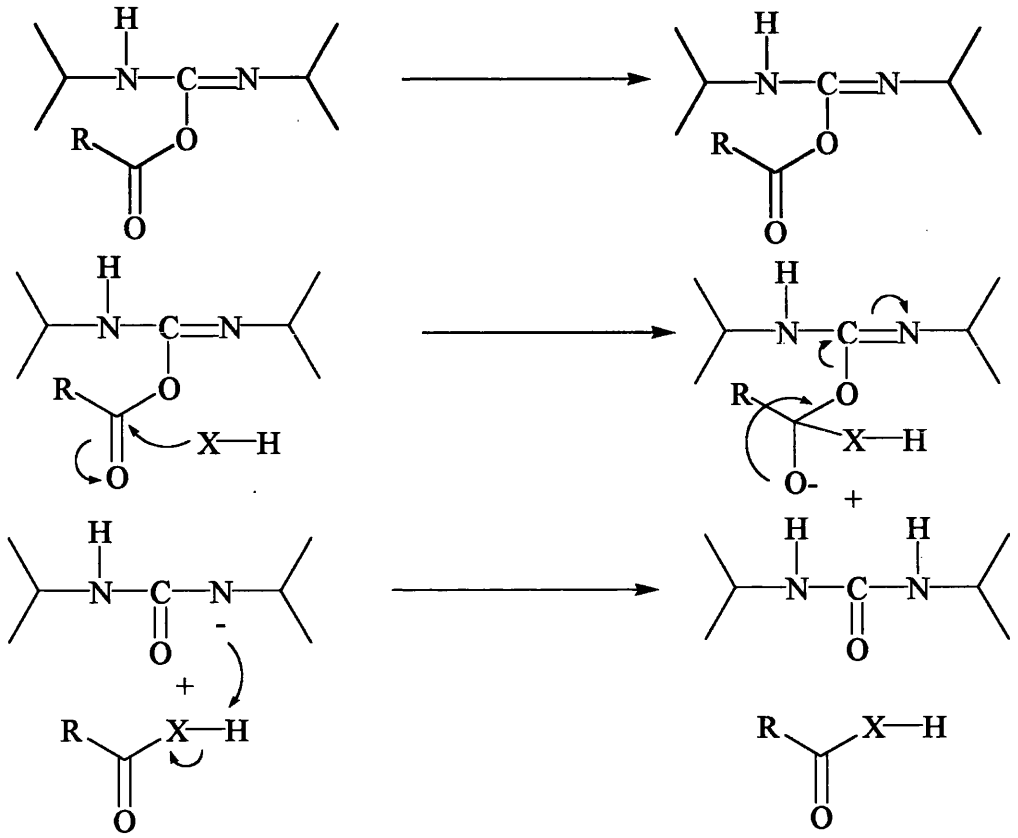
140 **141**



142 HOBt **143** DIPCDI **144** Fmoc-gly

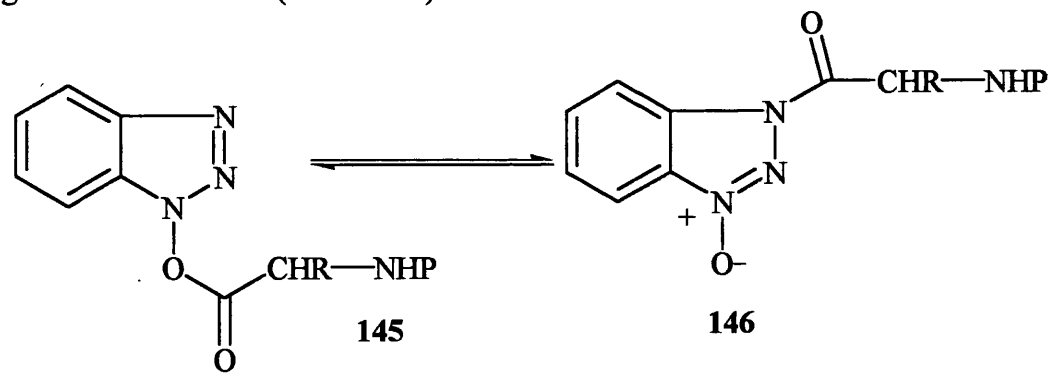
Scheme 42

Carbodiimides act as dehydrating agents removing a molecule of water between CO_2H and X-H where X is usually N or O to give an ester or an amide (Scheme 43).



Scheme 43

Amide coupling can take place using only a carbodiimide. However it is found that if HOBt is added racemisation and coupling times are reduced.[81,82] In this case the reaction is between the active ester of HOBt and the amino acid. The HOBt active ester **145** formed during the reaction has been isolated, and in solution has been proved to be in equilibrium with the regioisomer amide **146** (Scheme 44).[80]



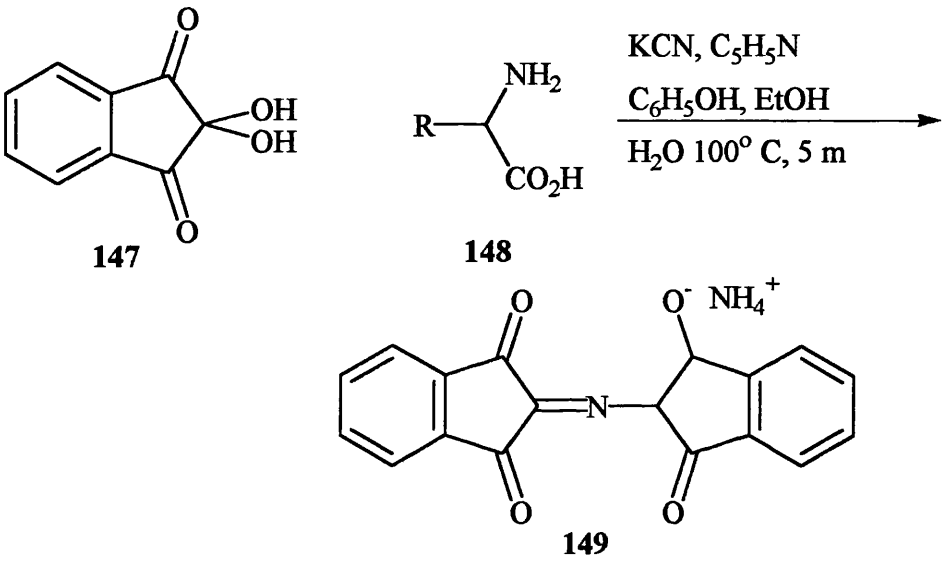
145 **146**

Scheme 44

(xiii) Monitoring of the reaction

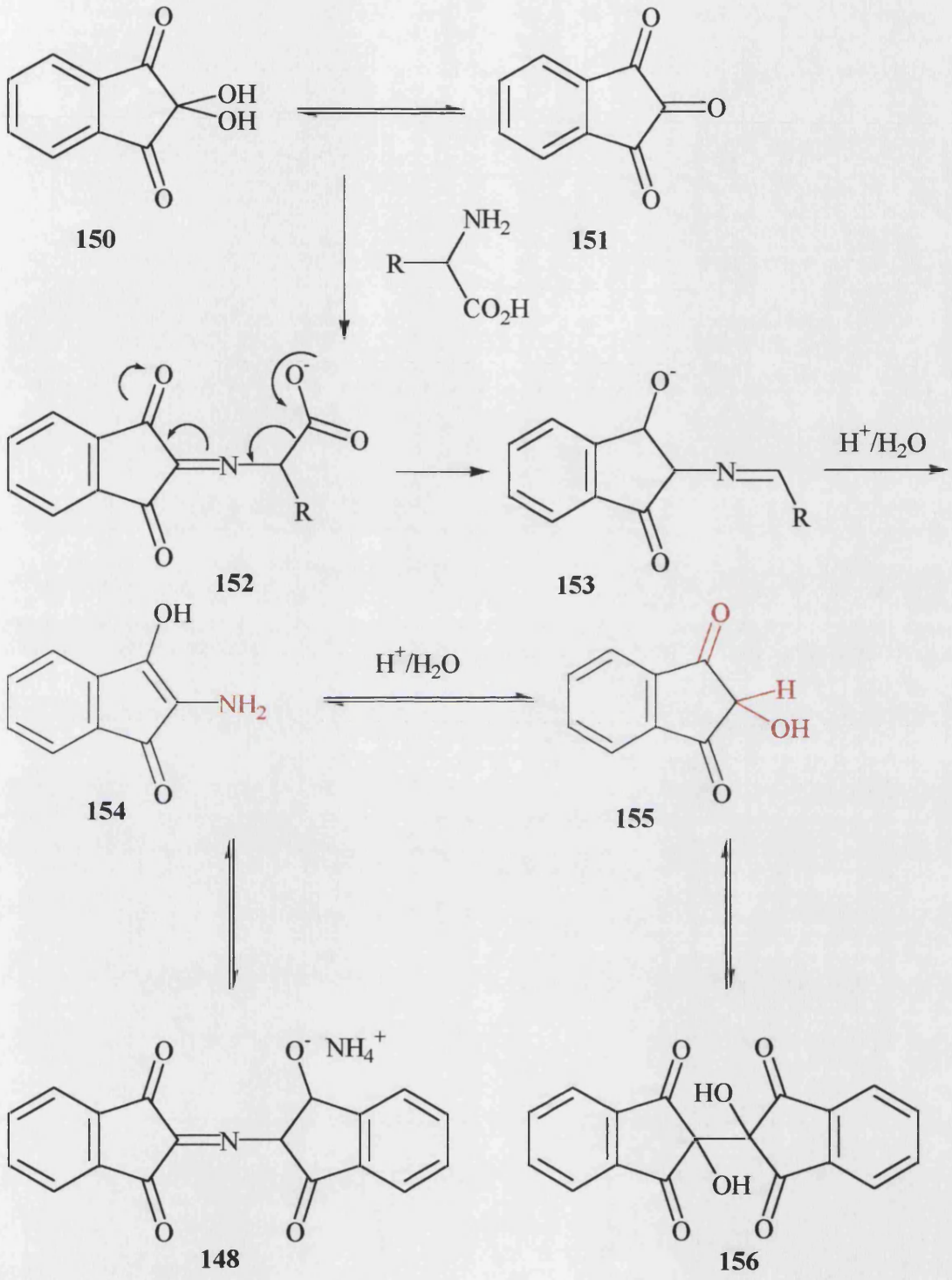
The presence of the NH_2 groups was monitored using the Kaiser test.[21]

The Kaiser test is a ninhydrin based test where the resin is heated with ninhydrin, KCN, phenol and pyridine. If an amine is present a purple or blue colour is formed. The colour formed is called Ruheman's purple (Scheme 45).



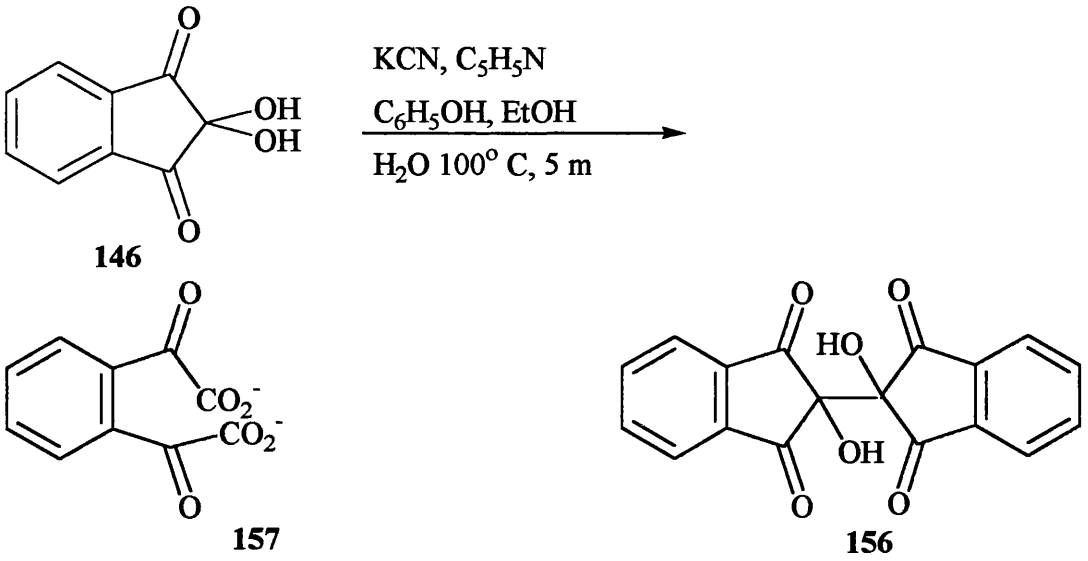
Scheme 45

The mechanism for this reaction has been documented (Schemes 46 and 47).[83]



Scheme 46

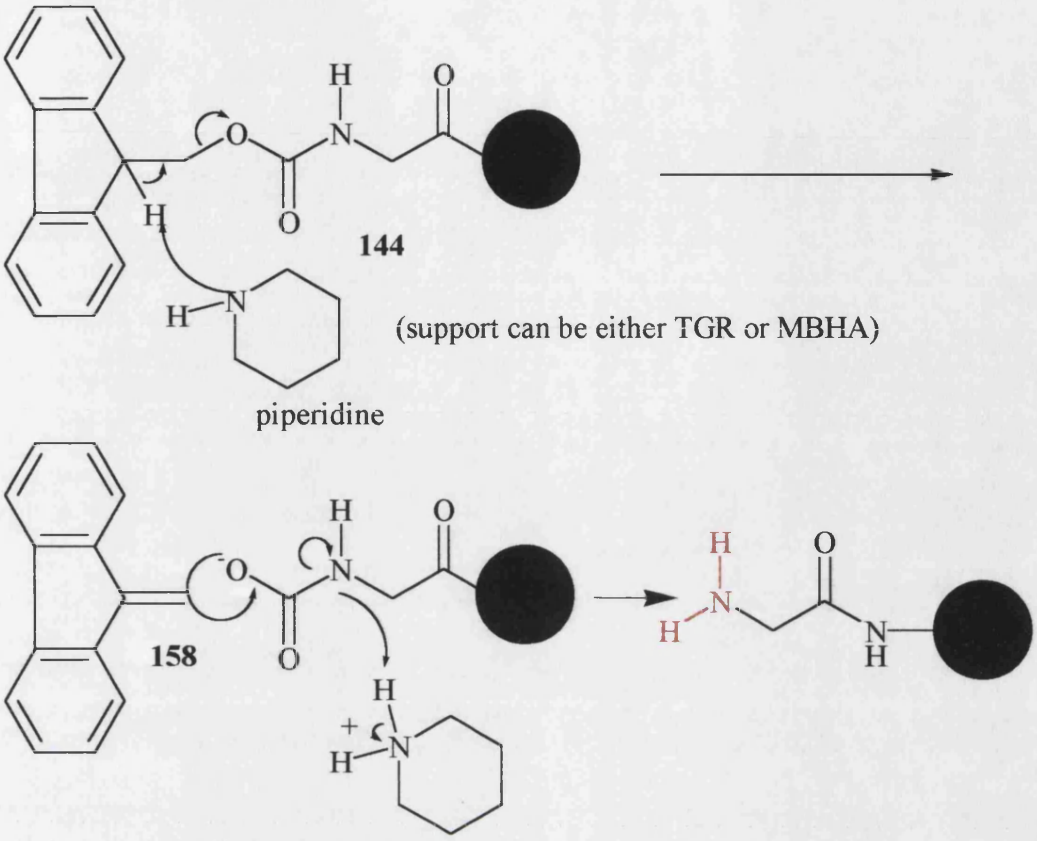
In the presence of nucleophiles such as cyanide, ninhydrin disproportionates to give hydrindantin **157** and phthalonic acid **156** (scheme 47). As all the above reactions are reversible excess hydrindantin drives the reaction to give Ruheman's purple.



Scheme 47

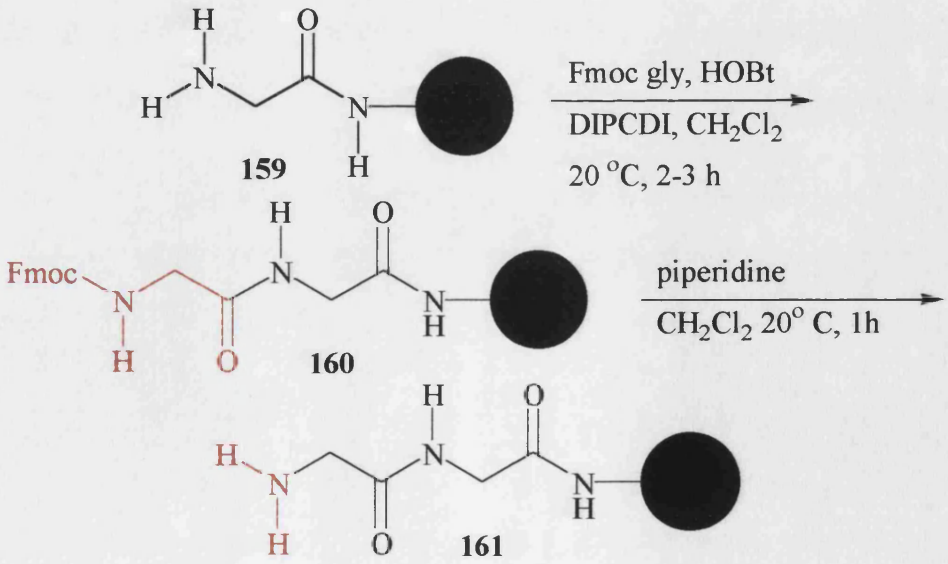
(xiv) Deprotection of the chain

After formation of the amino acid resin, the Fmoc group was removed by using piperidine. The Fmoc group could be deprotected by using any secondary amine but the advantage of using piperidine is that Fmoc-piperidine adduct can be seen by UV spectroscopy allowing the loading of the resin to be calculated. The other advantage is that the alkene **158** formed from the Fmoc cleavage can alkylate NH_2. If piperidine is used, however, the alkene reacts with piperidine removing it from the reaction (Scheme 48).[84]



Scheme 48

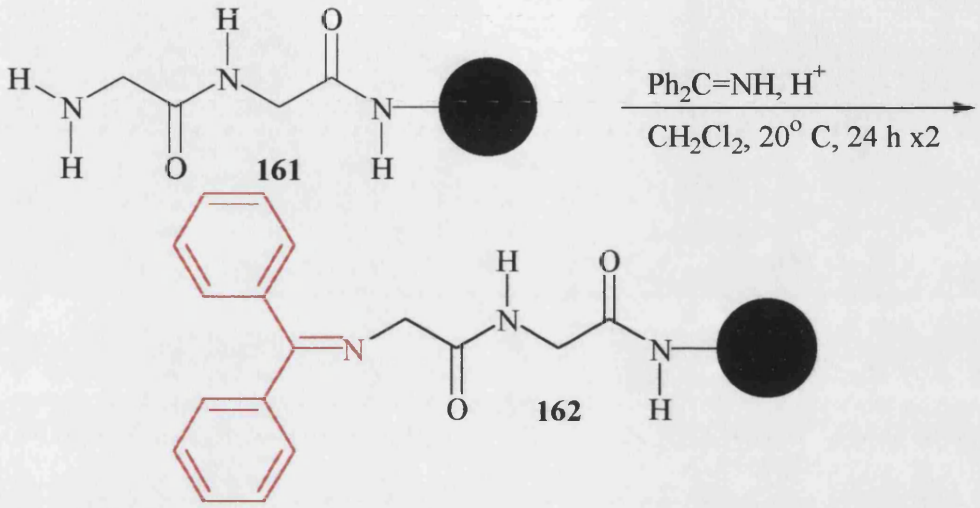
After the deprotection of the amino acid resin, the resin chain was extended by using the same methodology as before (Scheme 49).



Scheme 49

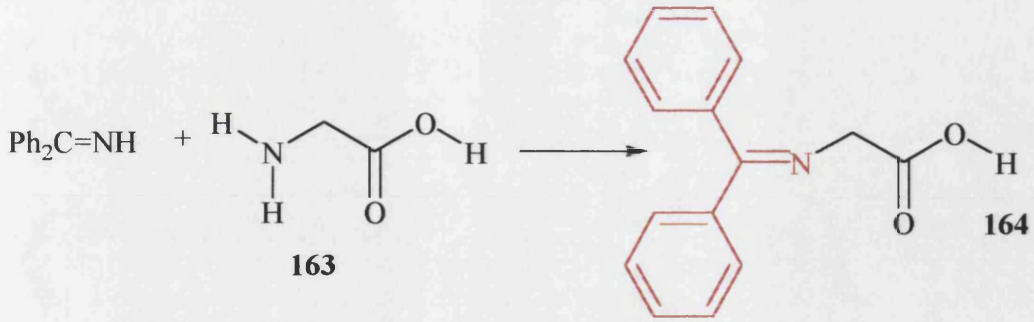
(xv) Formation of the imine

The imine was then formed by shaking with benzophenone imine and a catalytic amount of ethanoic acid. The reaction took a long time - at least a reaction time of 24 hours, repeated at least once was needed for the reaction to go to completion (Scheme 50).



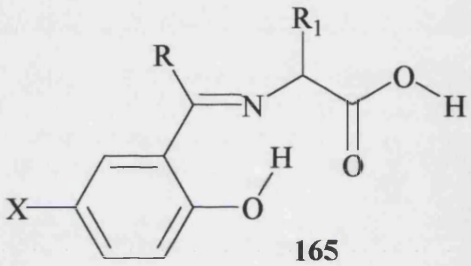
Scheme 50

The formation of the imine went to completion with the TGR, but with the Rink amide the formation of the imine never went to completion, despite repeated couplings and prolonged reaction times. The different results for the two different resins could be because of the differences in the solid support. TGR has a Tentagel chain between the polystyrene support and linker and because of this the resin swells much more on contact with the solvent. This means that the Tentagel almost "dissolves" in the solution, allowing more contact between the growing end of the chain and the reagents. MBHA on the other hand is just a polystyrene support and linker and therefore does not swell so much. An attempt to make the imine of glycine prior to coupling was unsuccessful (Scheme 51).



Scheme 51

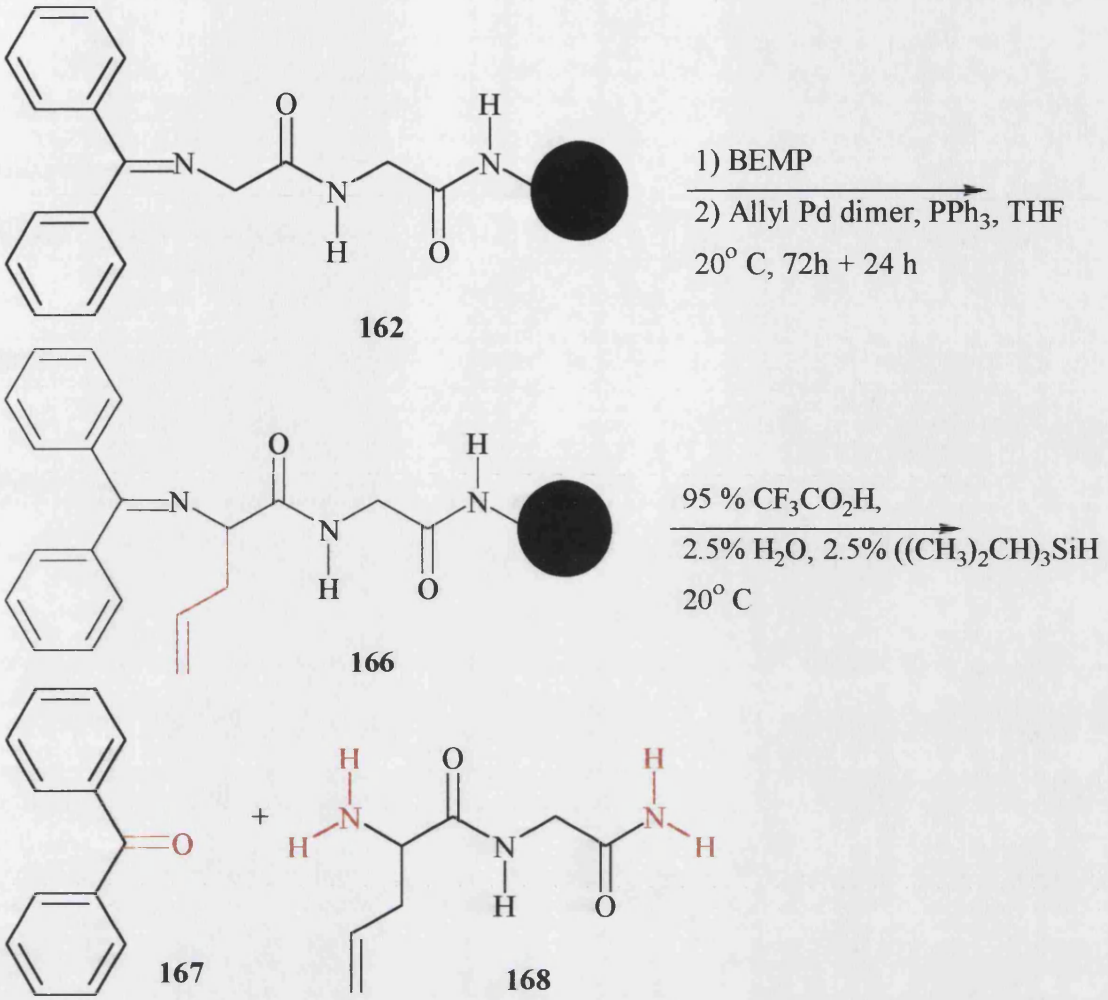
The failure of the above reaction was not surprising since although amino acids protected by imines derived from ketones have been reported in the literature,[85] they have all been made from o-hydroxy substituted aromatic ketones. The ortho hydroxy group is thought to stabilise the imine by H-bonding.[80]



R = Aromatic or Alkyl
X = Cl or Me

(xvi) Application of palladium chemistry to the resin

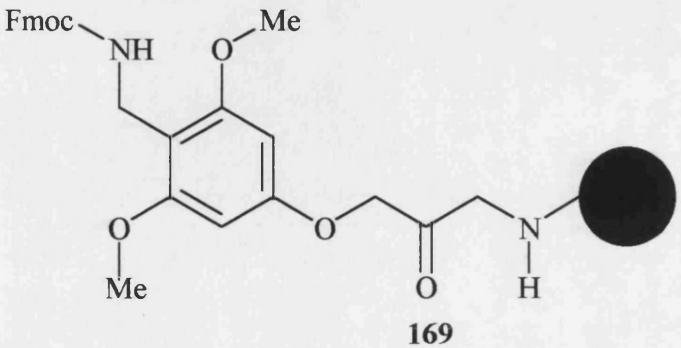
The palladium chemistry was then tried out on the glycine equivalent attached to the resin (Scheme 52)



162 **166** **167** **168**

Scheme 52

After the palladium chemistry was carried out the resin was cleaved to give a crude product, the ^{1}H NMR spectrum of which indicated that the product had been formed. This, however, was very impure and seemed to indicate that the imine had been removed from the amino acid by the cleavage conditions. As the product was so impure, it was decided to see how well the reaction would work with other resins. The next resin tried was PAL **169**.

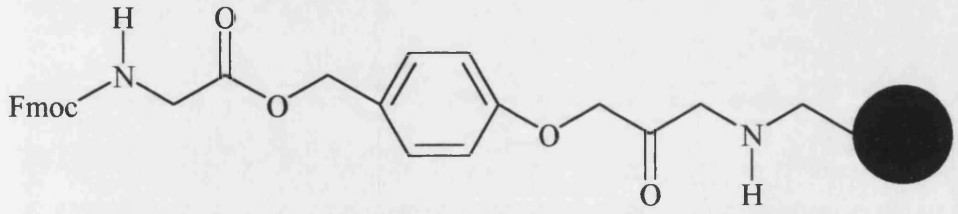


169

The loading of the amino acid on the resin and the formation of the imine were carried out as for the Tentagel resin without any problems. However this time the dipeptide was the compound on which the allylation was tested. Unfortunately the allylation did not succeed and so it was decided to investigate other resins.

(xvii) Investigation of other resins

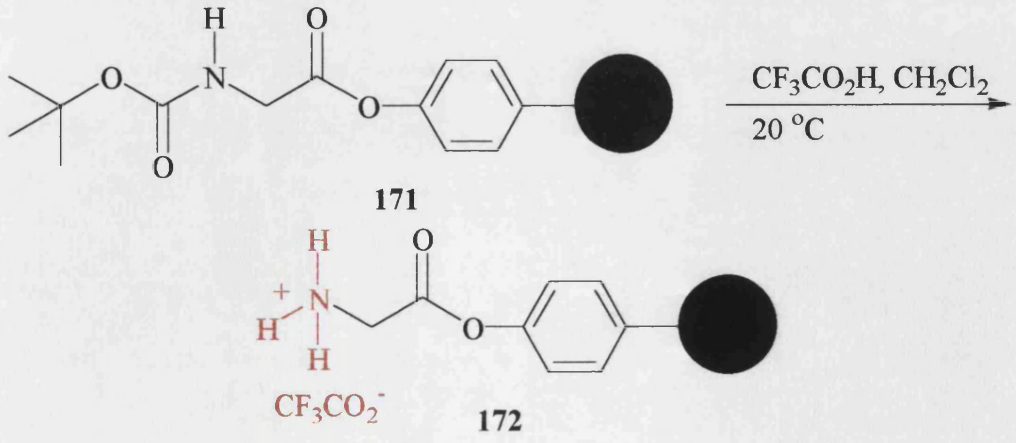
The next resin investigated was TGA (Tentagel acid) **6**. This was purchased as the Fmocgly resin **170**, which was then deprotected with piperidine prior to use.



NovaSyn TGA (Tentagel acid) resin **170**

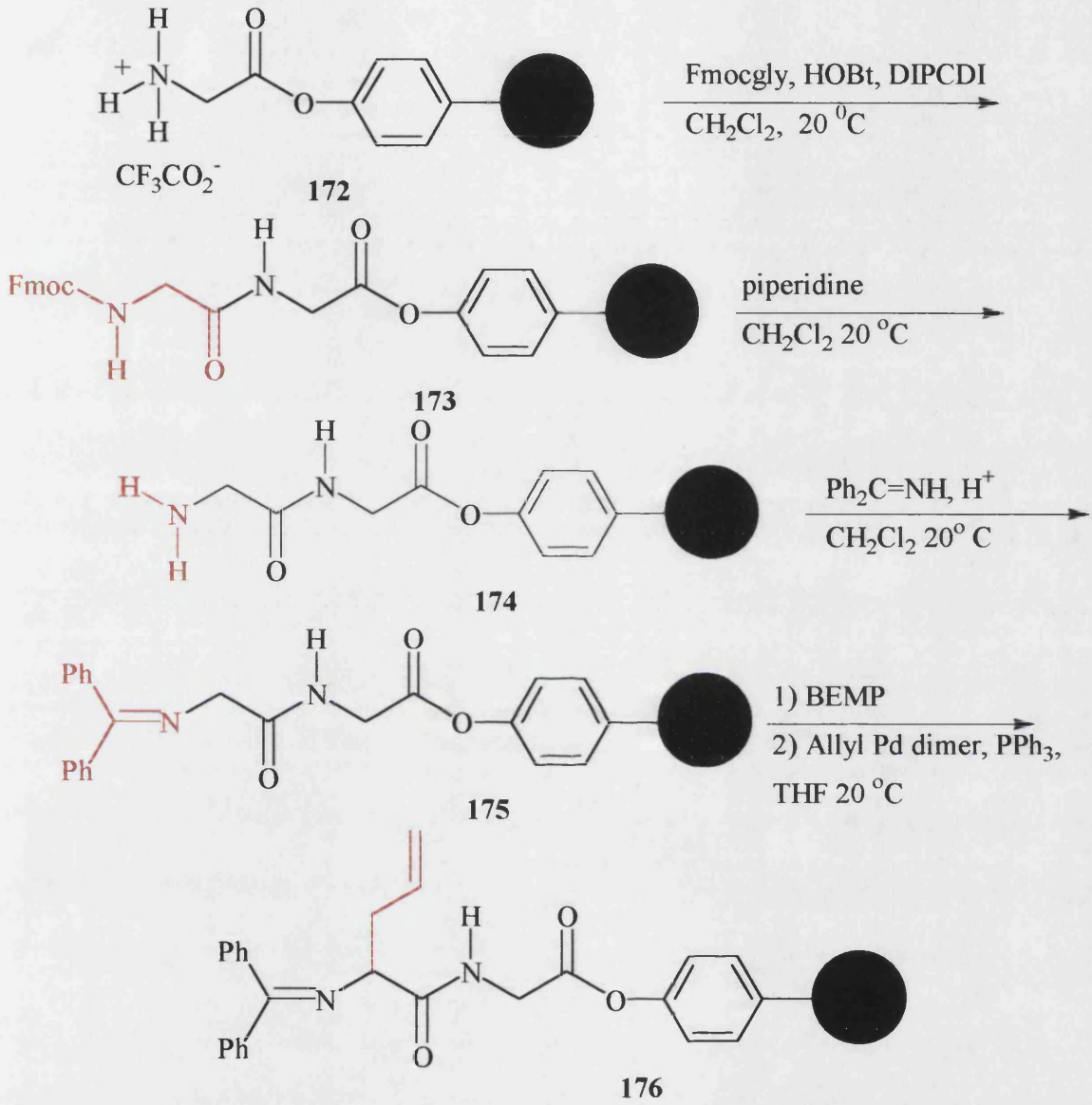
The formation of the amino acid and dipeptide imines occurred without any problems, following the same methodology as above. The allylation of the resin, however, did not give any product but we now consider that if this was repeated using the refined methodology (see later discussions) there would be a strong probability that this would be successful.

The next resin to be tried was Merrifield's resin **1**. This was purchased with ^{t}Boc glycine already attached **171** and deprotected before use with TFA (Scheme 53).



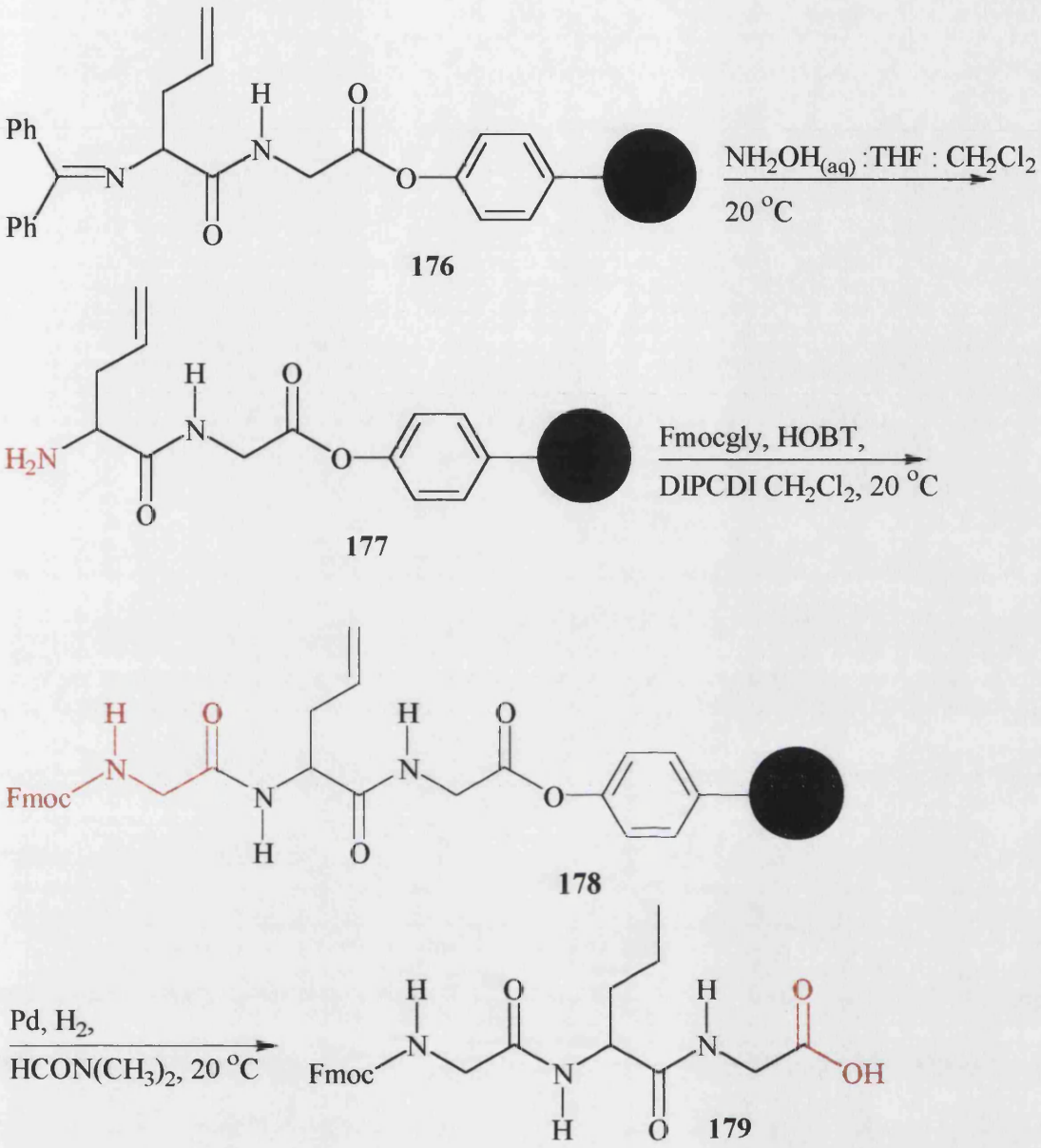
Scheme 53

The imine was formed as before and palladium chemistry carried out on the resin (Scheme 54).



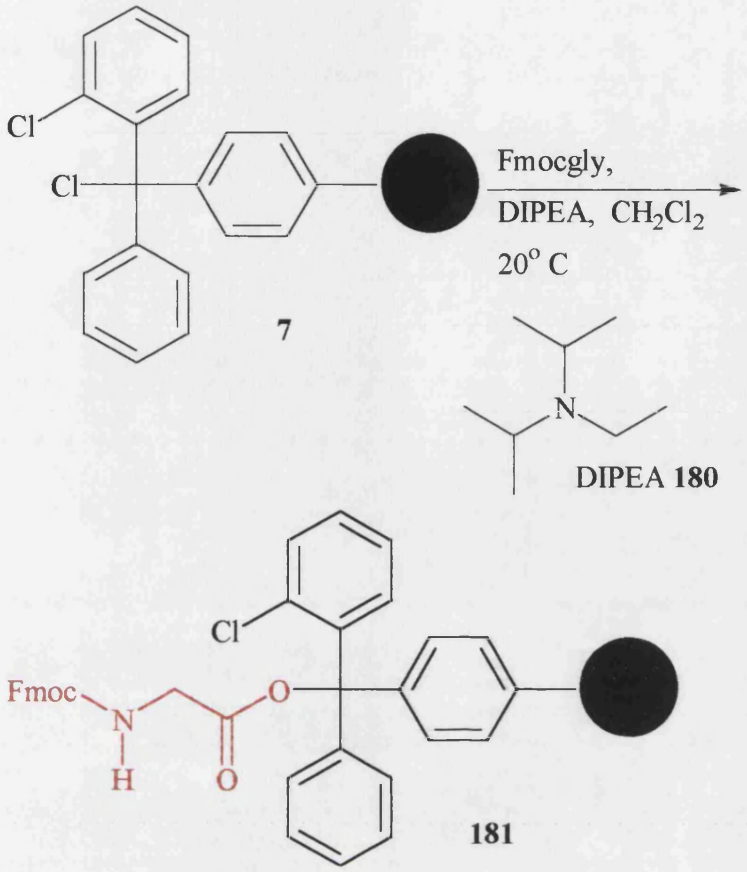
Scheme 54

To ensure that the product could be detected without too many problems the imine was removed using literature methods,[17] and an Fmoc glycine residue added to the resin to give a dipeptide with a much greater molecular weight (Scheme 55) than allylglycine on its own.



Scheme 55

Although the crude cleavage product seemed to resemble the desired material by ^1H NMR spectrum , attempts to repeat the reaction were unsuccessful. In addition the particular problems of working with Merrifield resin (see introduction) made it preferable to concentrate on 2 chloro trityl chloride **7** instead of Merrifield resin **1** - which gave much more successful results. The resin was loaded with the use of DIPEA as a base to neutralise the HCl produced as a side product (scheme 56).[8]



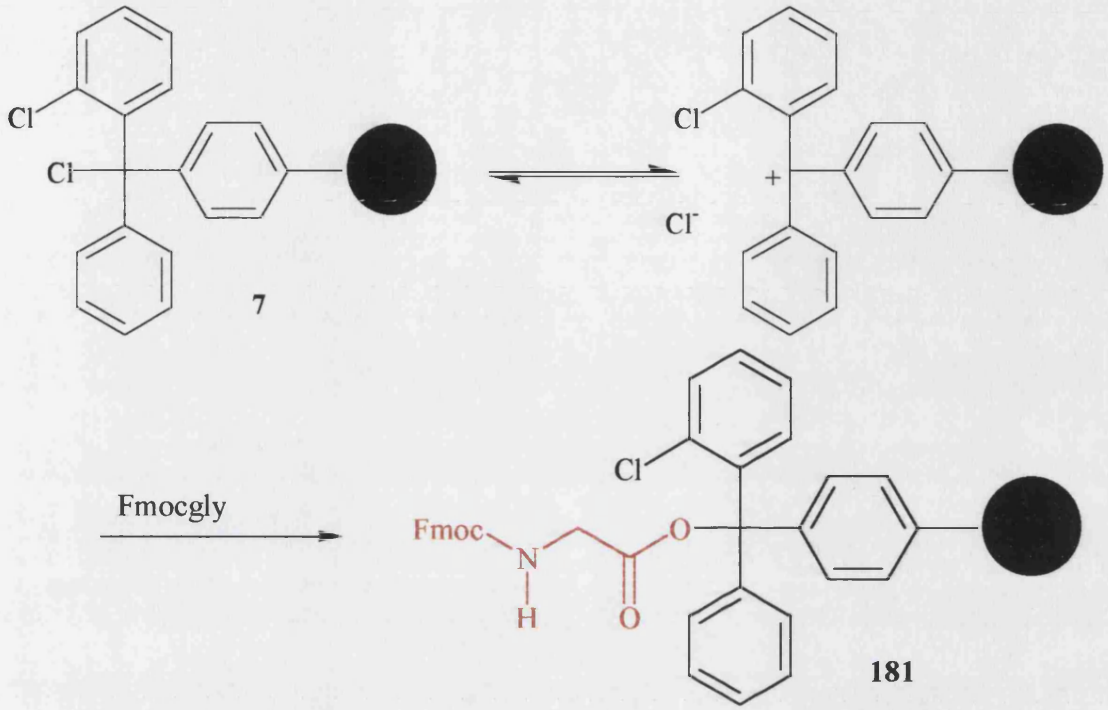
Scheme 56

The reaction is carried out by swelling the resin in DCM and then adding Fmoc amino acid/DIPEA solution to the resin and stirring for 90 minutes. It is then washed with methanol (to remove with any unreacted chloride) and other solvents and dried in a vacuum oven. The last solvent used is always DCM as this swells the resin and is volatile so it gives a swollen dry resin.

Tertiary amines are weaker bases than secondary amines and so DIPEA can be used without causing any deprotection of the Fmoc-gly-OH. They are weaker as bases as the replacement of the hydrogen with an alkyl group means that there is no opportunity for hydrogen bonding between the amine and substrate. Although the alkyl group is electron donating, this is more than offset by the lack of hydrogen bonding.

The reaction goes by an SN1 mechanism - the cation is stabilised by the three adjacent phenyl groups facilitating the loss of the chlorine (scheme 57). The loading is calculated by drying the resin and accurately weighing a small portion of it. The Fmoc protection group is

then cleaved by using piperidine and the concentration of the resulting piperidine-Fmoc adduct is measured by UV spectroscopy.



Scheme 57

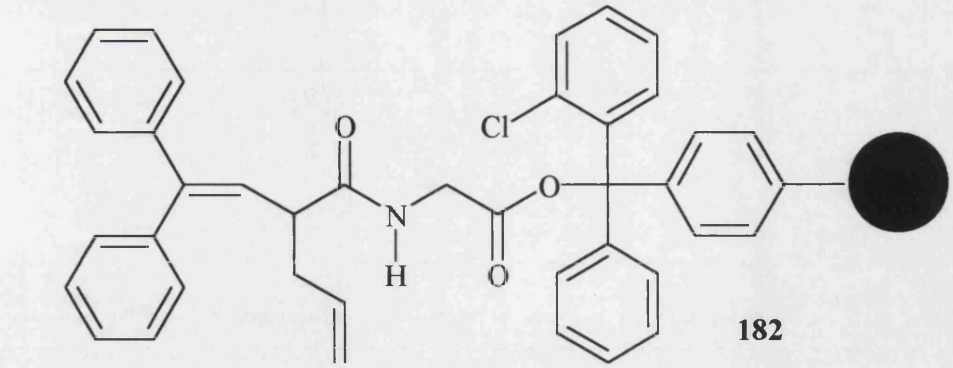
The amino acid chain was extended and the benzophenone imine was formed as above.

(xviii) Successful allylation of a glycine equivalent attached to a solid support

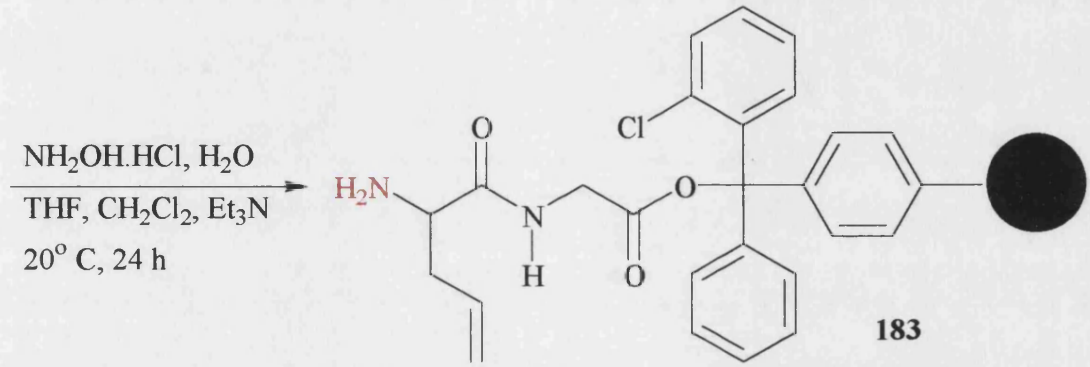
The palladium chemistry was carried out and the imine removed. The palladium chemistry was carried out by taking the dried resin and swelling in DCM (in later attempts to improve the reliability of the reaction different solvents were used). BEMP was then added and the reaction mixture was shaken for 10 minutes. The preformed palladium complex was added and the reaction left for 72 hours to ensure the completion of the reaction.

The imine was removed by using hydroxylamine solution (the hydroxylamine was used as the hydrochloride, with excess triethylamine present to neutralise it). Prior to cleavage

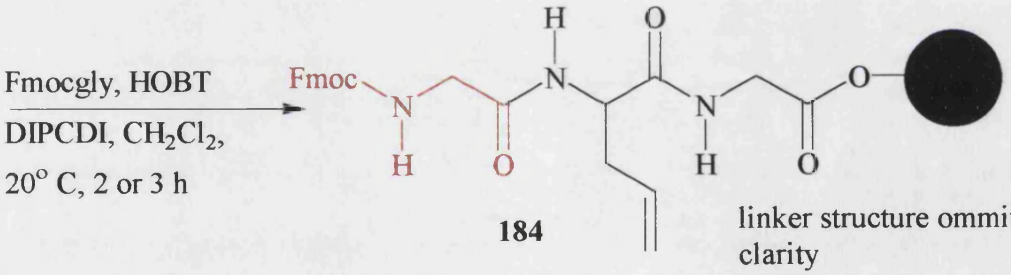
another Fmoc glycine residue was added to increase the mass of the product and to make purification and ^{1}H NMR spectrum identification easier (Scheme 58).



182

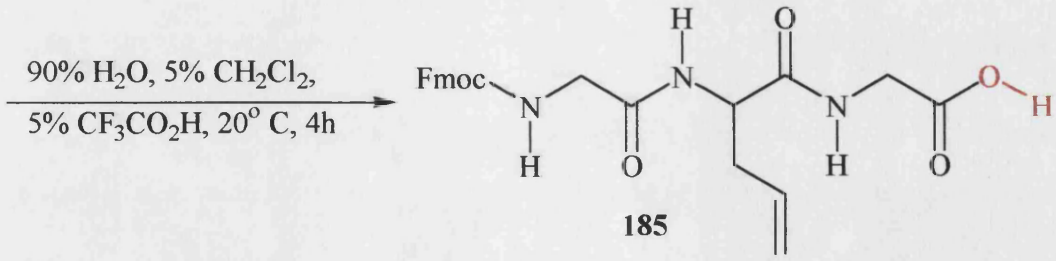


183



184

linker structure ommitted for clarity

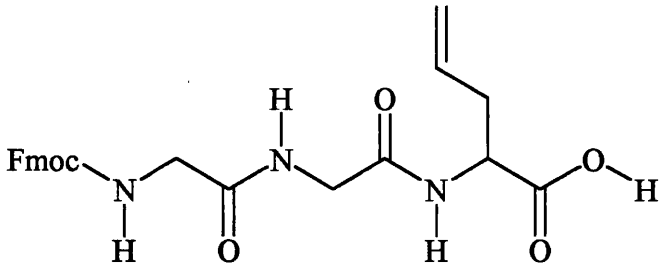


185

Scheme 58

The ^{1}H NMR spectrum of the pure compound (purified by preparative HPLC) had the distinctive allyl peaks 5.0 (2H, m, CH_2=CH), 5.7 (CH=CH_2) as did the ^{13} C NMR spectrum

117.5 ($CH=\mathbf{C}H_2$), 140.7 ($\mathbf{C}H=CH_2$), showing that either Fmoc-gly-allyglycine-gly-OH **185** or Fmoc-gly-gly-allylgly-OH **186** is the product.



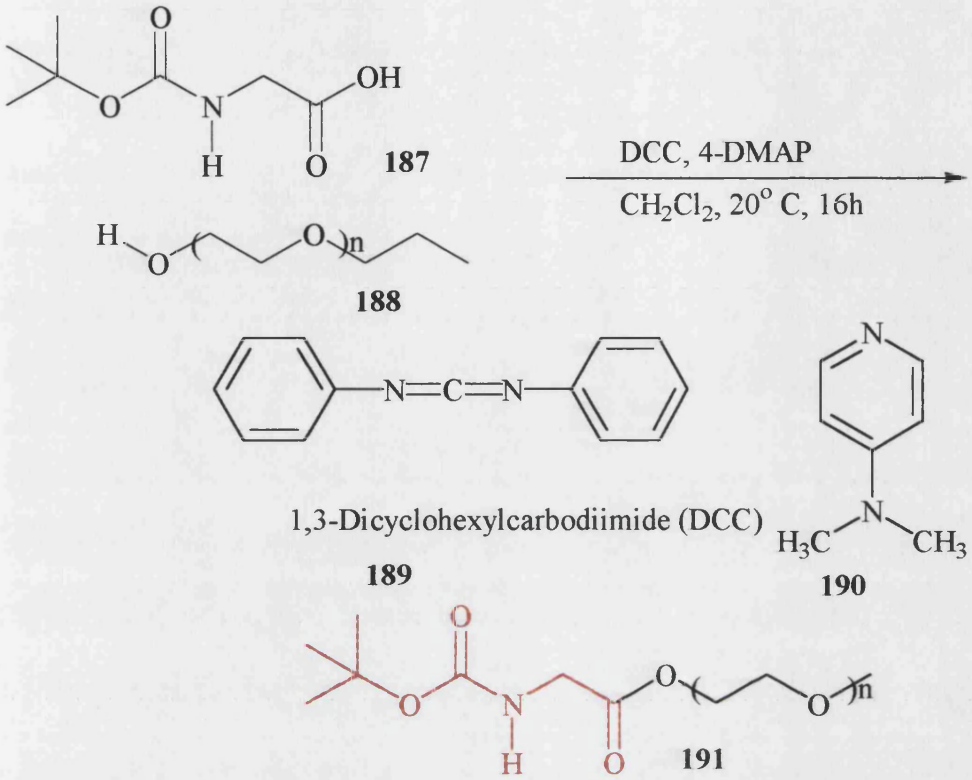
186

However the NMR spectra's for both **185** and **186** are so similar that it is difficult to say with certainty which was the product. Authentic material could have been produced to clarify this problem, but it was considered that this would be a waste of time, because, in solution phase work there was no allylation of the terminal glycine. This is even less likely to be the case when attached to a bulky resin.

(xix) Application of the work to liquid phase synthesis

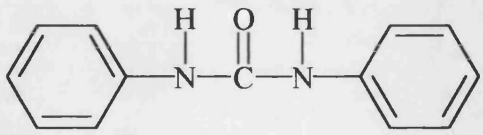
At the same time as this work was being undertaken on solid phase chemistry, the methodology was also being investigated using so-called "liquid phase" chemistry. This is a hybrid between solid phase chemistry (where the reaction takes place on a chain attached to a solid support) and solution phase chemistry (where the reaction takes place in a dissolved solution). In liquid phase chemistry the reactions take place on a support which is soluble in the reaction solvent (as in solution phase chemistry). The difference, however, is that on completion of the reaction, another solvent is added causing the material to crystallise. The support is then filtered and processed as if it were solid phase chemistry. According to the pioneers in this field, this is the ideal method for combinatorial chemistry.[24,25] My industrial supervisors at British Biotech asked me to try this because a) it might be helpful for my work and b) they wanted to have an unbiased opinion of it.

Firstly ^{t}boc-gly-OH **187** was loaded on the polyethylene glycol using DCC and DMAP (Scheme 59).



Scheme 59

In theory,[24,25] any insoluble reagents or side products such as DCU **192** can be filtered out of the CH_2Cl_2 solution and on subsequent addition of a small quantity of Et_2O the polyethylene glycol support crystallises.



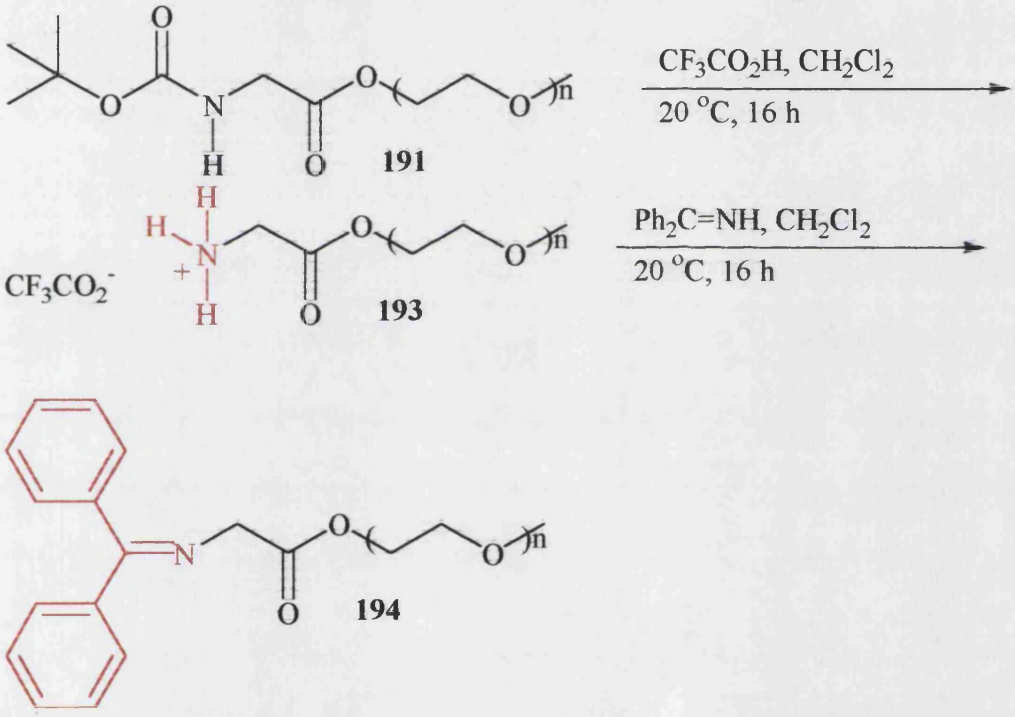
1,3-Dicyclohexylurea (DCU)

192

The polyethylene glycol can then be removed by filtration, giving the advantages of both solution and solid phase chemistry. In the literature it is suggested that addition of Et_2O produces immediate crystallisation. In practice, however, it required a large quantity of Et_2O

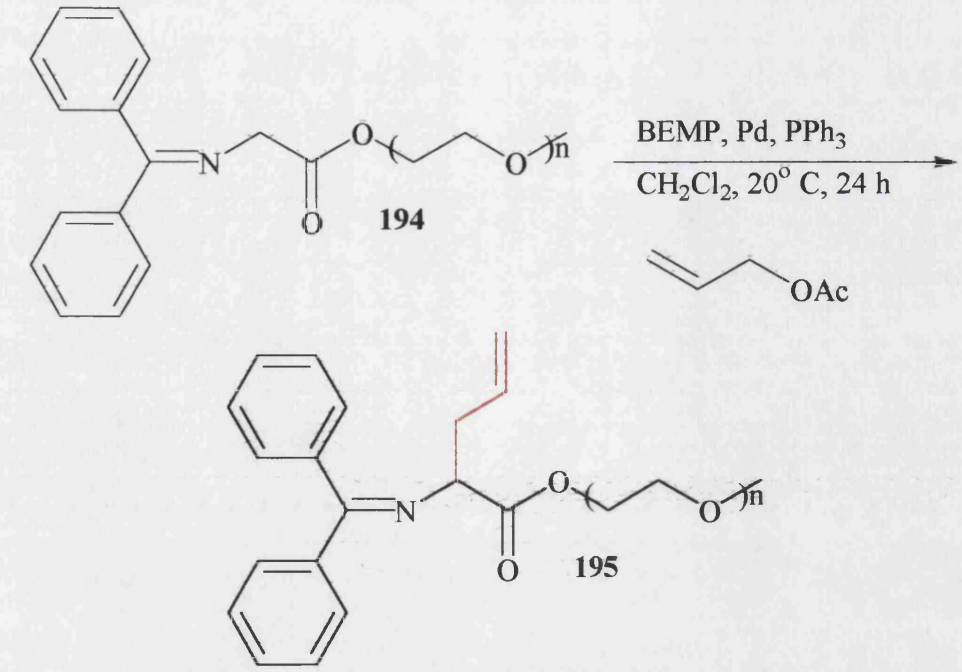
and cooling of the solution for the polyethylene glycol to crystallise. However it is possible that with further research this would be a useful technique and may even replace solid phase chemistry. Since this was not the subject of my research, however, only a brief investigation was carried out.

One considerable advantage of using liquid phase chemistry over solid phase chemistry was that it was possible to follow the reaction by ^{1}H NMR spectroscopy (the signal attenuation was increased so that the signal from the PEG was off the scale). The peak of interest was the ^{t}Boc group singlet in the ^{1}H NMR spectrum at 1.4 ppm. The ^{t}Boc group was removed by TFA and the imine was then formed (Scheme 60). After the formation of the imine ^{1}H NMR spectrum spectroscopy was not a useful method of following the reaction because it was difficult to gain any useful information from the spectra.



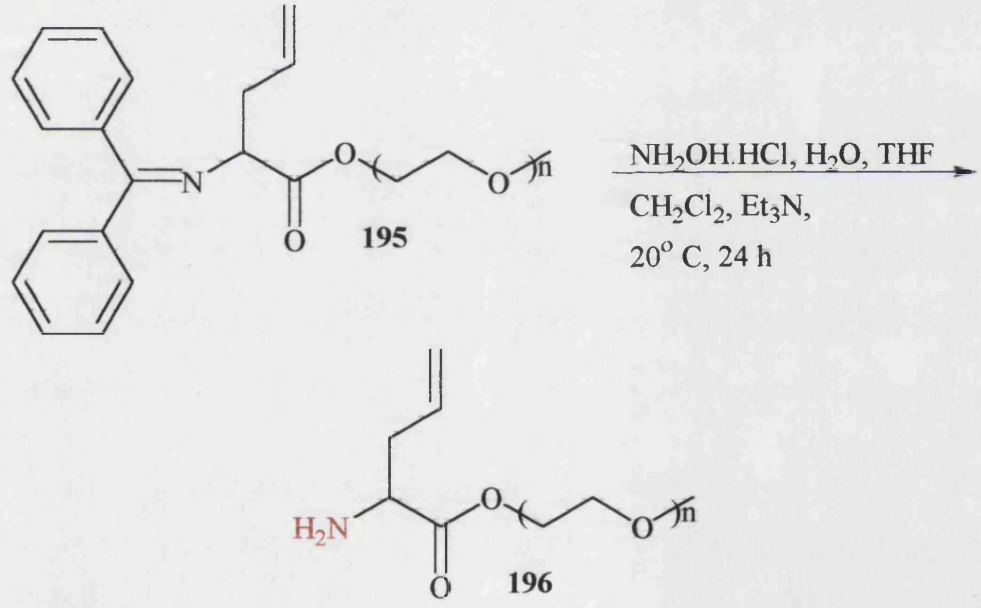
Scheme 60

The imine was subjected to palladium chemistry (Scheme 61) using the same methodology as before. It was, however, impossible to know for certain if the reaction had gone to completion due to the difficulty of monitoring the reaction.



Scheme 61

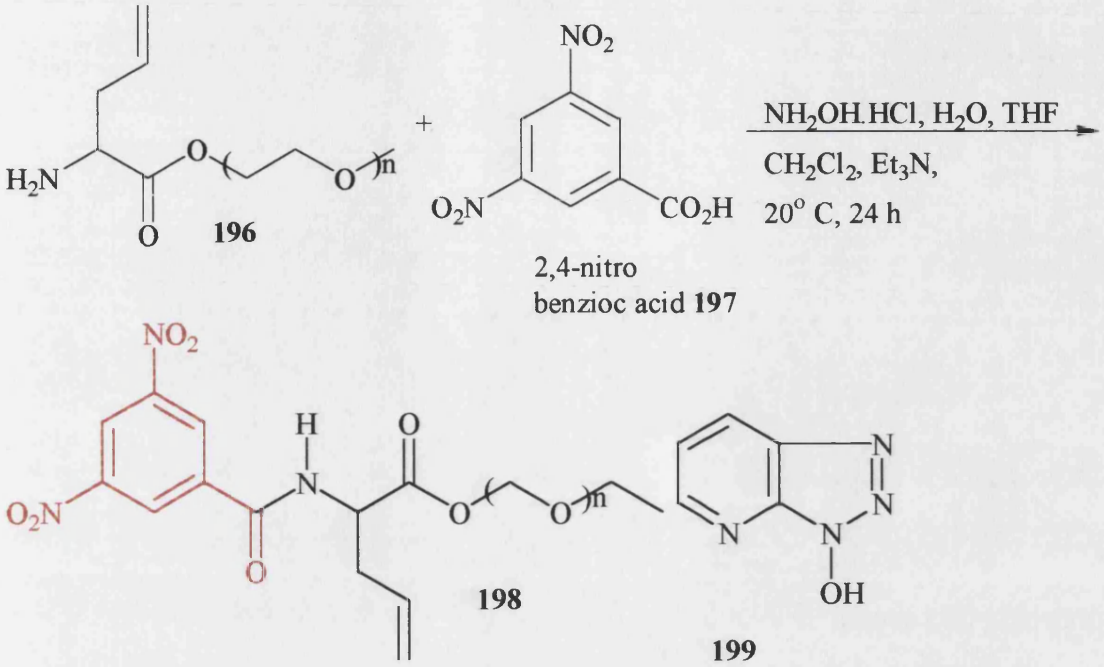
The imine was then cleaved (Scheme 62) using the same methodology as before.



Scheme 62

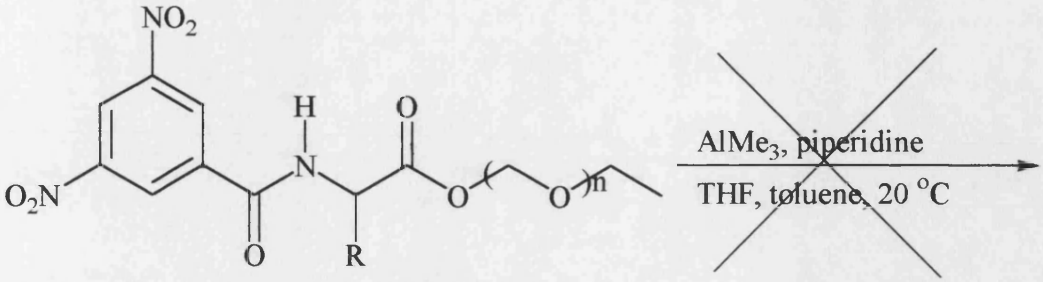
To increase the mass of the material prior to cleavage 3,5 dinitro benzoic acid was coupled to the amino acid (Scheme 63). The reaction was monitored by using the Kaiser test. In the reaction HOAt was used instead of HOBt because 3,5 dinitro benzoic acid does not undergo coupling reactions very well. This is because the electron withdrawing group on the

benzene ring reduces the electron density on the carbonyl carbon. HOAt is a much more effective coupling additive than HOBt and is generally used in difficult couplings such as this one.[86]

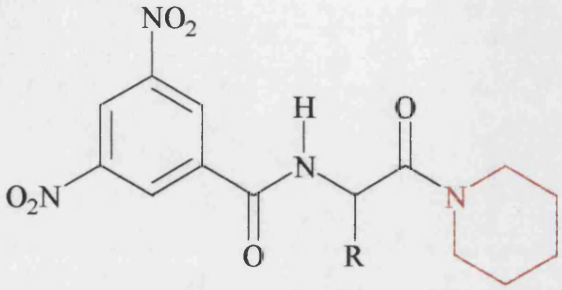


Scheme 63

Attempts to carry out transesterfication or transamidation with both allylated and unallylated materials according to literature methods,[87,88] were all unsuccessful however. (Schemes 64 & 65)

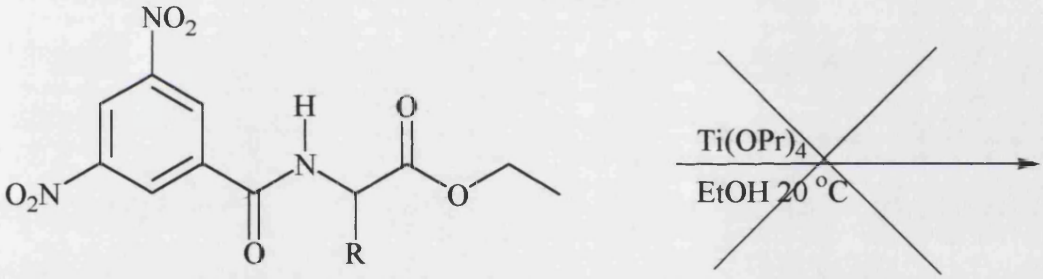


198 R = allyl
200 R = H

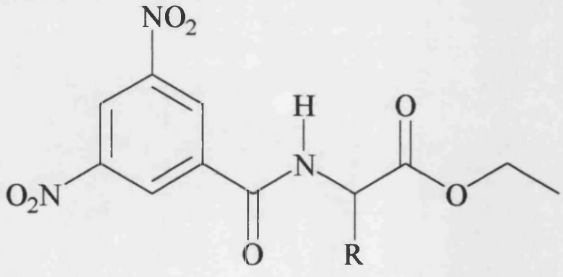


201 R = allyl
202 R = H

Scheme 64



203 R = allyl
204 R = H



205 R = allyl
206 R = H

Scheme 65

Since allylation of solid/liquid phase chemistry and liquid phase chemistry itself are both new techniques, it was decided to leave the investigation of liquid phase chemistry until

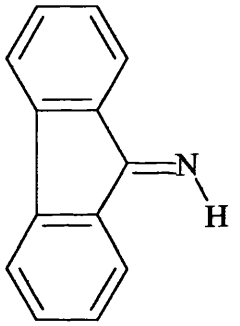
all the work had been carried out on solid phase chemistry. There were still some problems with the work carried out on imines synthesised on solid phase chemistry. These were :-

(i) reproducibility of the results.

(ii) formation of the imine.

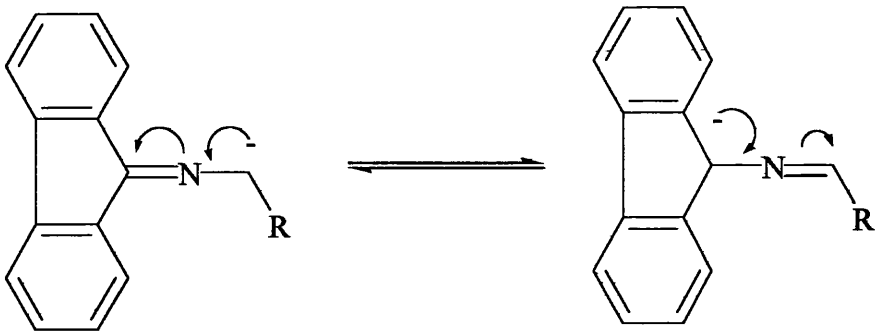
(xx) Investigation of 9-fluorenone imine and imines derived from it

Although vigorous exclusion of air and moisture helped to improve the reproducibility of the results, the reliability of the reaction was still not satisfactory. One possible solution to this problem, which might also have had other benefits, was to make imines using 9-fluorenone imine **207**.

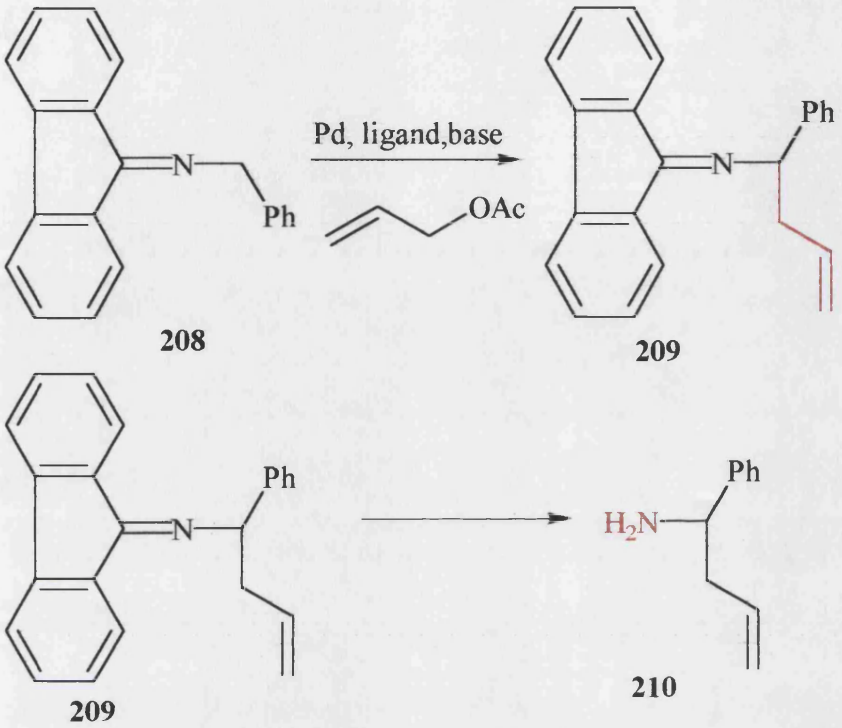


207

The reason for this is that imines derived from fluorenone imine are 10 pka units below those derived from benzophenone imine.[4] We thought that because the anion could be formed more easily the reaction would go better. The difference in behaviour between benzophenone and fluorenone derived imines is because of the formation of a π-14 electron delocalised planar system in the latter's anion. As this has 4n+2 π electrons it should be aromatic.[89]



The other benefits might have been the application of this methodology to β amino acids and the possibility of making potential nucleophiles for palladium phase compounds such as **208**. The imine could then be removed giving a NH_2-CH^--Ph synthon (Scheme 66).

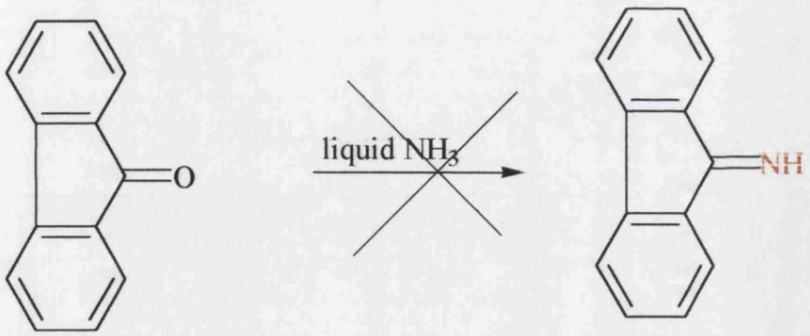


Scheme 66

The above methodology would also be a route into substituted benzylamines.

(xxi) Attempted synthesis of 9-fluorenone imine

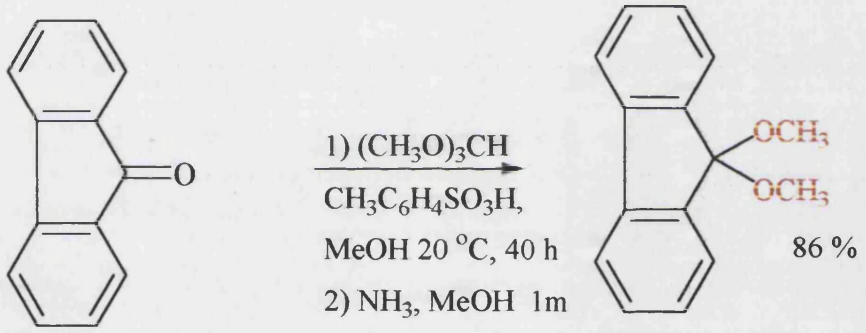
As 9-fluorenone imine **207** was not available commercially it was decided to synthesise it. The first method tried was unsuccessful (Scheme 67).[90]



211 **207**

Scheme 67

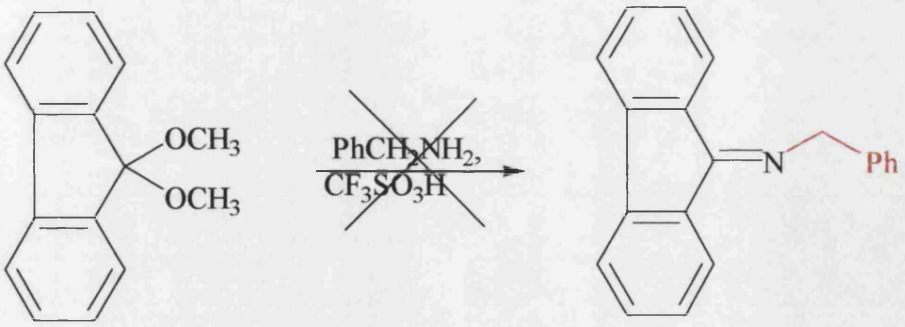
After hearing about results from the Heaney group in connection with making imines from acetals,[91] it was decided to repeat their work. This method was particularly attractive as the first compound in the synthesis - fluorenone acetal **212** - is a known compound.[92] It was decided to test the viability of the methodology by making the known compound **208** from **212** (Schemes 68+69).[93]



211 **212**

Scheme 68

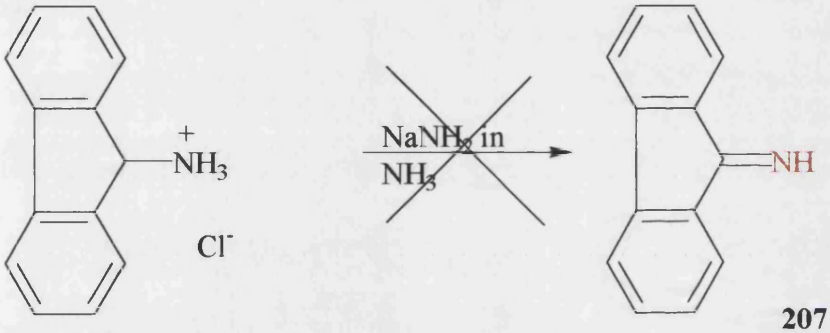
The reaction to form the acetal **212** was successful giving fluorenone acetate **212** in a good yield (86%) as a yellow solid. The identity of the product was confirmed by analysis of the ^{1}H NMR spectrum which showed the characteristic methoxy signal at 3.3 ppm which was comparable to the literature value.[93] An attempt to make *N*-(9H Fluorene-9-ylidine) benzyl **208** from the acetal was then tried (Scheme 69).



212 **208**

Scheme 69

Unfortunately, however, this was not successful. Another literature method was tried (Scheme 70)[94] which was also unsuccessful.

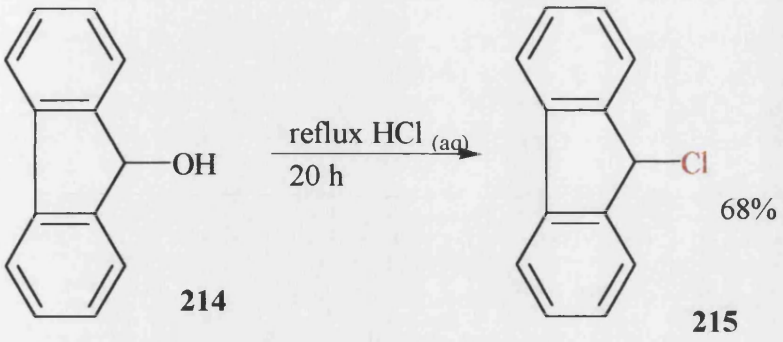


213 **207**

Scheme 70

(xxii) Successful synthesis of 9-fluorenone imine

Fortunately the third literature method which was tried (Schemes 71-73) was successful.[95] Firstly 9-hydroxyfluorene was converted into the chloride by heating with concentrated HCl solution (Scheme 71). Although we could have purchased 9-bromofluorene and used that instead, it was cheaper to make the chloride. In addition it was preferable to follow the whole of the literature method just in case the bromide and chloride gave different products, although this is unlikely as the C-Br is weaker and more reactive than the C-Cl bond and so should form the azide more easily than the chloride.

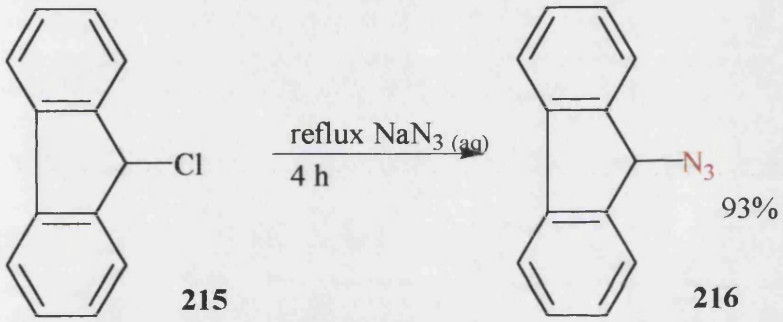


214 **215**

Scheme 71

The reaction went well giving 9-chlorofluorene **215** product in moderate yield (68%) as a colourless solid. In the ^1H NMR spectrum there was no sign of an O-H signal.

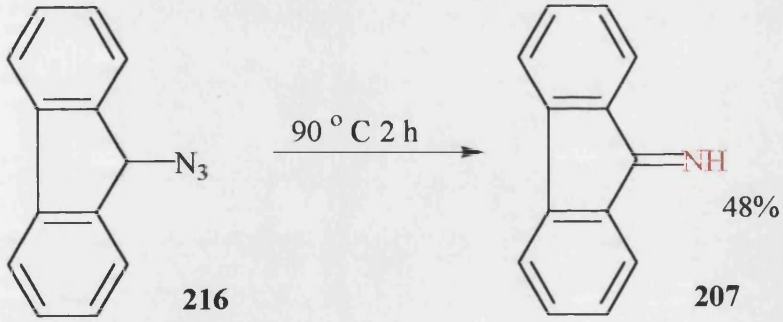
It was then converted into the azide **216** by means of an nucleophilic substitution reaction with NaN_3 (Scheme 72).



215 **216**

Scheme 72

Heating the azide causes it to decompose into the imine (Scheme 73).

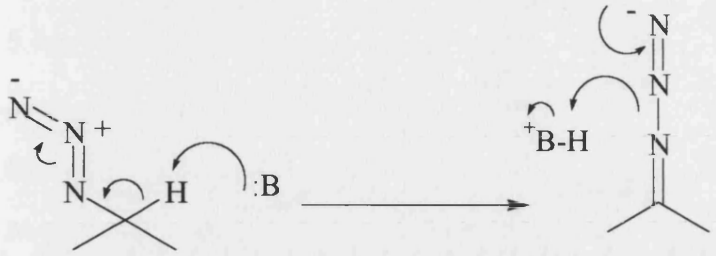


216 **207**

Scheme 73

The formation of 9-fluorenone imine **207** went well giving the product in moderate yield (48%) as a brown solid. The IR showed aromatic C-H stretches at 3000 cm^{-1} and C=N stretch at 1449 cm^{-1}.

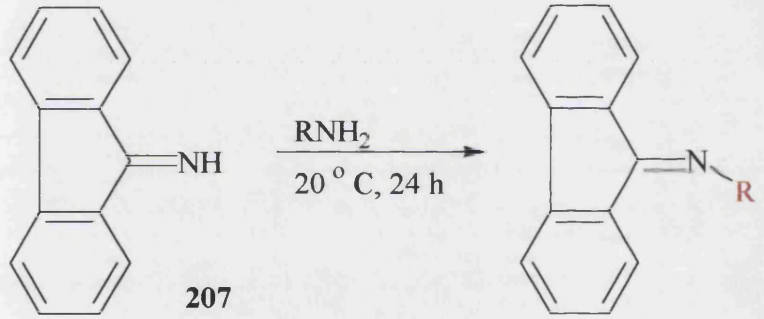
A mechanism for the decomposition of **216** was not suggested in the literature. It probably takes place by the mechanism shown below, however; the imine itself could act as the base and if this were the case the reaction would be auto catalytic (Scheme 74).



Scheme 74

(xxiii) Synthesis of imines derived from 9-fluorenone imine

The imines shown below were synthesised using the method of O'Donnell *et al* (Scheme 75) from 9-fluorenone imine.[4]



207

208 R = CH_2Ph 60%
217 R = $CH_2CH_2CH_3$ 84%
218 R = $CH_2CH_2CO_2CH_2CH_3$ 74%
219 R = $CH_2CONHCH_2CO_2CH_2CH_3$ 66%

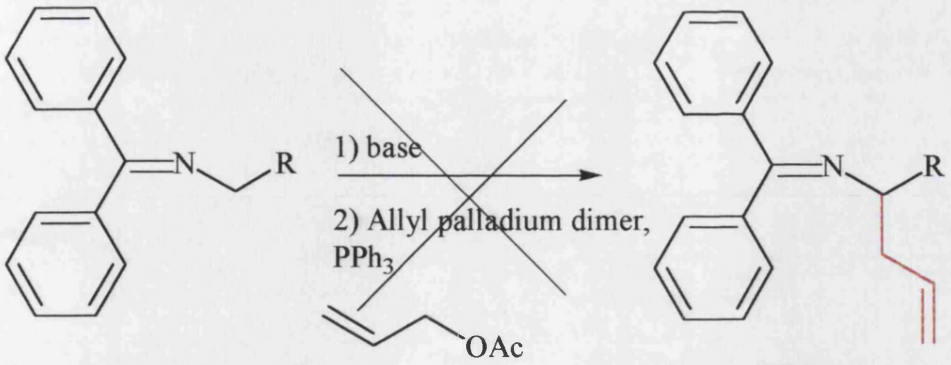
Scheme 75

The reactions were successful with a moderate yield (60%) for *N*-(9H fluorene-9-ylidine) benzenemethanamine **208** which was an orange solid. The yield for *N*-(9H fluorene-9-ylidine) propylamine **217** was good (84 %) and the product was an orange oil. The yield for *N*-(9H fluorene-9-ylidine) propylamine **218** was good (74 %) and the product was a yellow solid. The yield for *N*-(9H fluorene-9-ylidine)-gly-gly-OEt **219** was moderate (66 %) and the

product was a yellow solid. The crystal structure was analysed by x-ray crystallography. Neither compound was stable on either silica or alumina TLC sheets. The identity of the products was confirmed by analysis of the ^{1}H NMR spectrum which showed the characteristic methylene signal adjacent to the imine moiety at different values for every compound :- 5.4ppm **208**, 4.09 ppm **217**, 4.36 **218** and 4.33 **219** for both compounds. The corresponding peak was less variable in the ^{13}C NMR spectrum:- 56.7ppm **208**, 55.7 ppm **217**, 60.3 **218** and 61.5 **219** for these compounds. In the case of *N*-(9H fluorene-9-ylidine) propylamine **217** and *N*-(9H fluorene-9-ylidine) benzenemethanamine **208** these values were the same as in the literature.[93] The accurate mass and CHN for *N*-(9H fluorene-9-ylidine)-gly-gly-OEt **219** were similar to the expected values, for (Found: M^+ 322.1313, $C_{19}H_{18}N_2O_3$ requires M^+ 323.1317), (Found: C 70.3 %, H 5.58 %, N 8.53 % $C_{18}H_{22}N_2O_3$ requires 70.8 %, 5.60 % and 8.70 %). As *N*-(9H fluorene-9-ylidine) propylamine **217** and *N*-(9H fluorene-9-ylidine) benzenemethanamine **208** are known compounds the accurate masses for these were not taken. Unfortunately it was impossible to crystallise *N*-(9H fluorene-9-ylidine) β alanine ethyl ester amine **218** to purify it in order to obtain an accurate CHN and it did not give an accurate mass using our mass spectroscopy systems.

(xxiv) Attempts to allylate imines derived from 9-fluorenone imine

Palladium allylation of all four substrates was attempted (Scheme 76), but proved unsuccessful. This could be because the pK_a of the substrates was too low for the anions to be good nucleophiles. According to the literature the pK_a of imines derived from fluorenone is about 10 pK_a units lower than the same imine from benzophenone imine.[4] It was therefore concluded that fluorenone imines would not be a fruitful area for allyl palladium chemistry research.

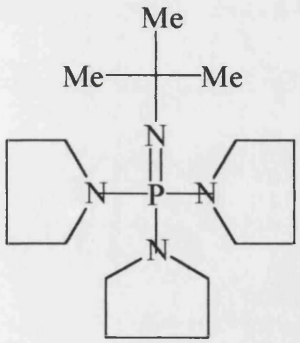


Base = LDA
NaH
KH
LDA/K^{t}BuO
BSA/KOAc
BEMP

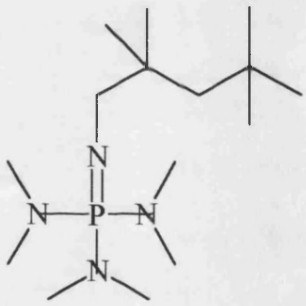
208 R = CH_2Ph
217 R = $CH_2CH_2CH_3$
218 R = $CH_2CH_2CO_2CH_2CH_3$
219 R = $CH_2CONHCH_2CO_2CH_2CH_3$

Scheme 76

It was then decided to use alternative phosphazene bases in the solid phase chemistry such as BTTP(tert-butylinino-tri(pyrrolidino) phosphorane **220** or tert-octylimino-tri(dimethylamino) phosphorane **221** in order to compare their effectiveness with BEMP **37**.



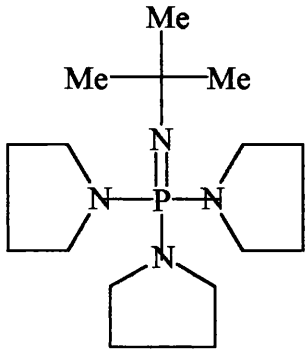
220 BTTP



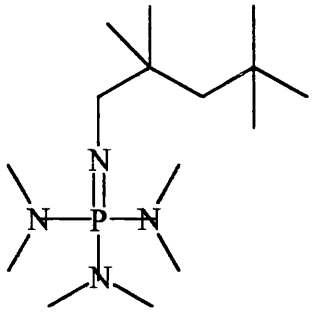
221 phosphazene base

There was, however, no improvement in the reaction. It was found that they worked as effectively, but no better than BEMP **37**. This information was useful, however, as **217** and **217** are substantially cheaper than **37** although less stable.

It was then decided to use alternative phosphazene bases in the solid phase chemistry such as BTTP(tert-butylinino-tri(pyrrolidino) phosphorane **220** or tert-octylimino-tri(dimethylamino) phosphorane **221** in order to compare their effectiveness with BEMP **37**.



220 BTTP

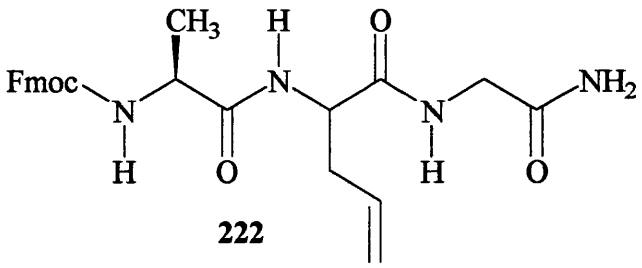


221 phosphazene base

There was, however, no improvement in the reaction. It was found that they worked as effectively, but no better than BEMP **37**. This information was useful, however, as **217** and **217** are substantially cheaper than **37** although less stable.

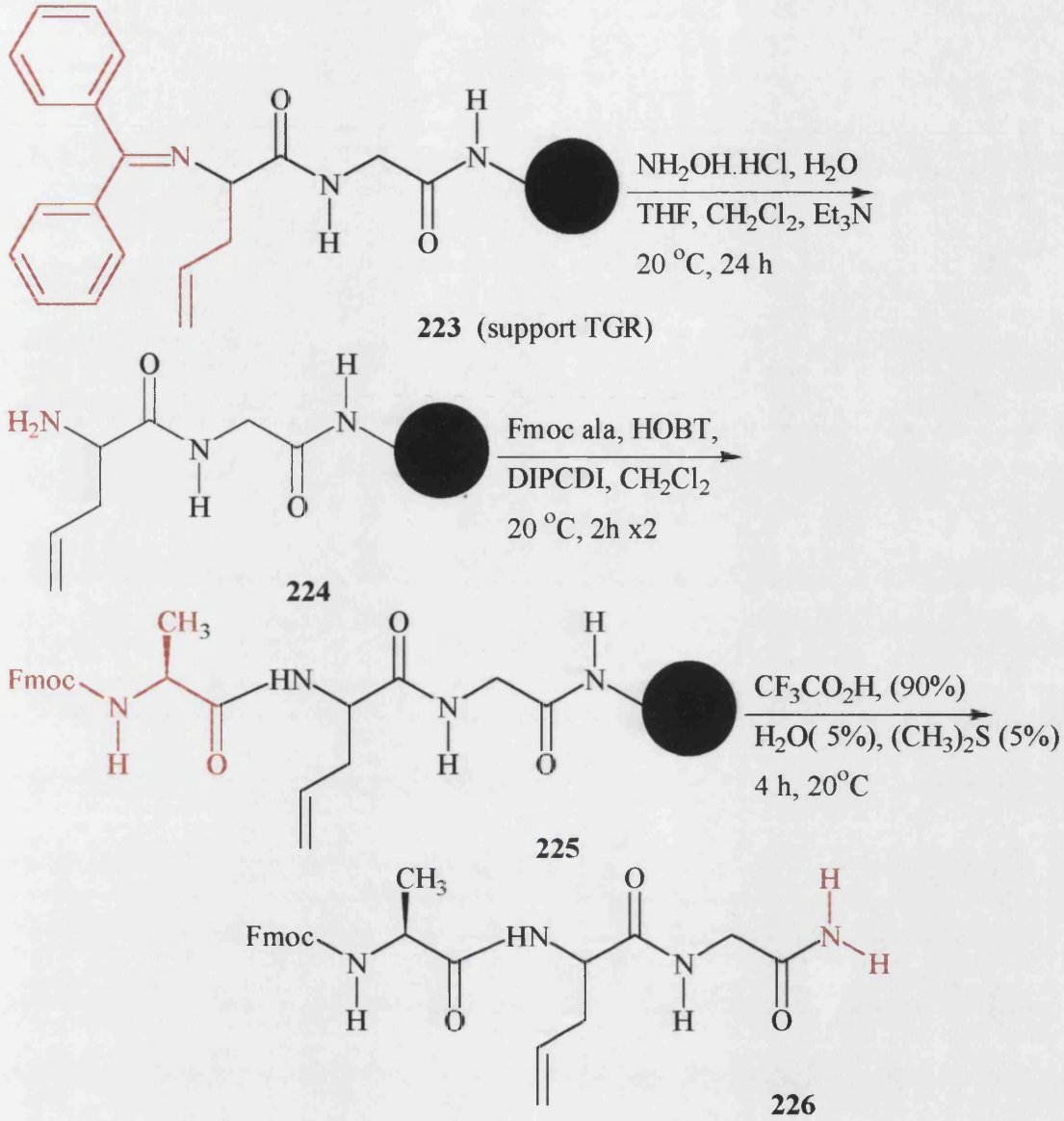
(xxv) Reinvestigation of Tentagel rink amide

By this stage in the research the expertise in solid phase chemistry had improved so that it was decided to reinvestigate the use of **12**. This time it proved quite successful, forming the Fmocala-allyl-gly-glyamide **222**.



222

The palladium chemistry was carried out on the resin as before. However this time when the imine was removed the chain was extended with Fmoc-ala-OH, instead of Fmoc-gly-OH to give the peptide amide **222** (scheme 77).

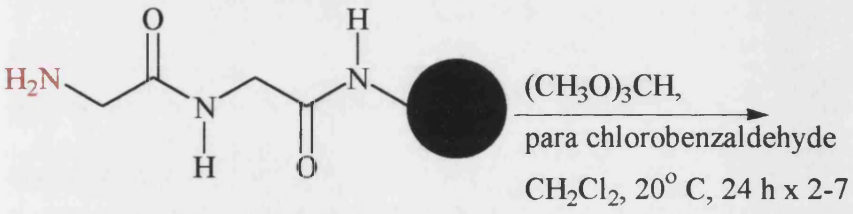


Scheme 77

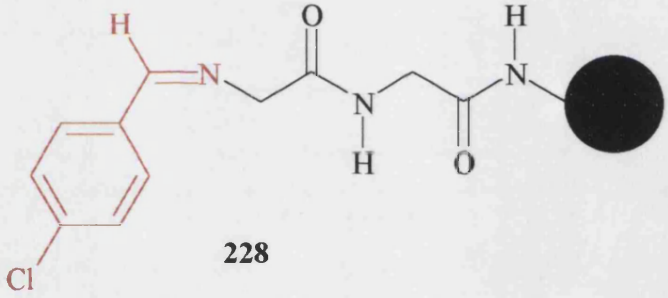
A different cleavage cocktail (CF_3CO_2H 90 %, H_2O 5%, $(CH_3)_2S$ 5%)[96] was used which could be partially responsible for the improved results. An advantage of this cleavage cocktail is that it is easily removed *in vacuo*. The disadvantage is that DMS is a particularly foul smelling compound to work with. DMS and water are used as cation scavengers to remove the cations formed as side products to the acid cleavage.

(xxvi) Use of different imines

As the formation of the imine sometimes required many repeated reactions (sometimes 7 x 24 hours) on both **7** and **12**, it was decided to use para-chlorobenzaldehyde instead of benzophenone imine to activate the amino acid (Scheme 78). In the solution phase chemistry the advantage of benzophenone derived imines is that they are stable and can be columned. However, this stability is not the most important advantage in solid phase chemistry; the most important consideration is that the reaction goes to completion reliably.



227 (support TGR or 2Cl TrCl)



228

Scheme 78

The formation of the imine worked better with both resins going to completion in half the time of the benzophenone imine. It had the added benefit that the starting material was less expensive. The reaction times, however, were still variable, particularly with resins derived from **7**. This could have been because the loading of the resin was variable, and therefore the concentration of the reagents was also variable. It was noticed that the higher the loading of the resin the longer the reaction time.

Different solvents/mixtures of solvents were then investigated to see which solvent systems worked most effectively. The solvent systems tried were CH_2Cl_2, DMF, THF, and a DMF /CH_2Cl_2 mixture where DMF was used to form the Pd complex and CH_2Cl_2 to swell

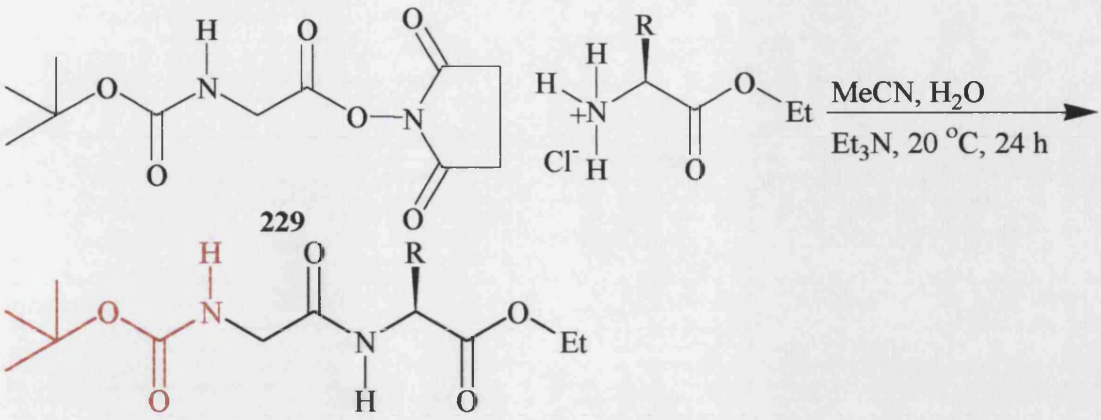
the resin. The results with pure THF were the most reproducible while those with CH_2Cl_2 were the most variable. It was unlikely that this was because of moisture in the DMF or CH_2Cl_2, since reactions carried out in parallel from the same source of solvent gave different results despite using an identical source of resin and solvent. The DMF was purchased as anhydrous from Aldrich while the CH_2Cl_2 was dried by distilling over $CaSO_4$ prior to use.

All the previous work took some time to carry out because the reaction was temperamental and various conditions had to be investigated to improve the reaction. It is now thought that the reason for the unreliability of the reaction was because the resin is hydrophobic and so small quantities of water may have been trapped inside the resin affecting the palladium catalyst. In retrospect a Karl Fischer analysis could have been used to test this theory. If the theory had been proved to be correct, it might have been possible to remove the water prior to use by washing or heating with a solvent such as toluene. Another possibility would have been to run the reactions with a dehydrating agent present to remove any trace of water.

The next areas of research in solid phase chemistry were to see:- (i) the effect of a neighbouring amino acid on the stereochemistry, (ii) the effects of different ligands on yield and de (or ee), and (iii) the scope of the reaction with different electrophiles. In addition the effect of different solvents on stereocontrol was investigated .

(xxvii) Synthesis of dipeptides

The neighbouring amino acid effect in solution phase chemistry also needed to be investigated. To make the substrates for this research, three dipeptides were synthesised, using N-hydroxysuccinimide active esters (Scheme 79).[97]



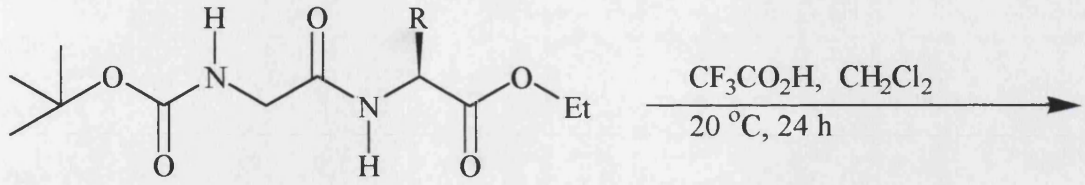
229

230 R = CH_3 85%
231 R = CH_2Ph 70 %
232 R = $CHCH_2(CH_3)_2$ 98%

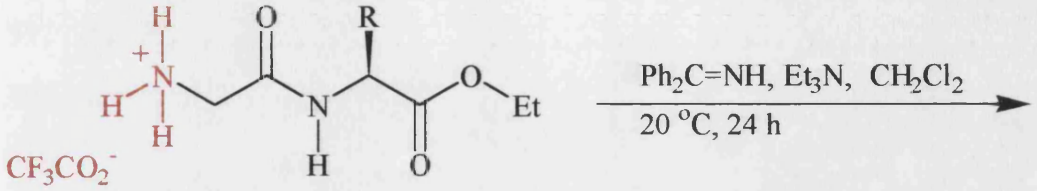
Scheme 79

All the ^{t}Boc protected dipeptides produced were oils. These were purified by sequentially washing with NH_4Cl solution, $NaHCO_3$ solution, and water, then drying with $MgSO_4$ and finally removing the solvent in *vacuo*. The reaction went well with good to excellent yields; - 70% for ^{t}Boc-gly-L-phe-OEt **231**, 85 % for ^{t}Boc-gly- L-ala-OEt **230**, and 98.5 % for ^{t}Boc-gly-L-leu-OEt **232**. The ^1H and ^{13}C NMR spectrum's were satisfactory, with the CH_2CON signal being very similar for all the compounds - 3.83 ppm **230**, 3.75 ppm **231** and 3.8 ppm **232**. Accurate masses were not obtained for the ^{t}Boc protected dipeptides because of the instability of these compounds in FAB or Electron spray mass spectroscopy. However, they were obtained for the imines or allylated imines (see later).

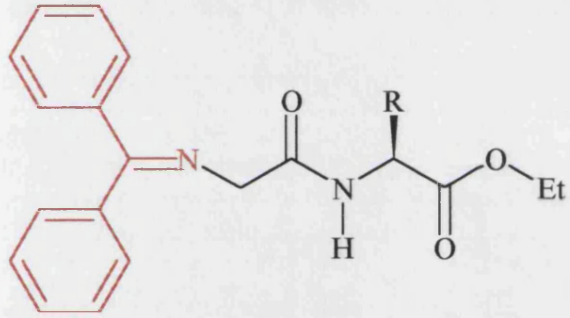
The ^{t}Boc dipeptides were deprotected with CF_3CO_2H and the crude product made into the imine (Scheme 80).



230 R = CH_3
231 R = CH_2Ph
232 R = $CHCH_2(CH_3)_2$



233 R = CH_3
233 R = CH_2Ph
234 R = $CHCH_2(CH_3)_2$



235 R = CH_3 69%
236 R = CH_2Ph 73%
237 R = $CHCH_2(CH_3)_2$ 57 %

Scheme 80

The reaction for *N*-(diphenyl methylene)-gly-L-ala-OEt **235** went well affording an oil in 69 % yield. The ^{1}H and ^{13} C NMR spectrum were satisfactory with the characteristic CH_2=N singlet appearing at 4.0 and 61.3 ppm respectively. The side chain CH_3 appeared at 1.4 and 14.0 or 18.6 ppm respectively. We did not undertake a C-H correlation to distinguish between the two methyl groups in the ^{13} C NMR spectrum. In the ^{1}H NMR spectrum they were distinguished by looking at the *J* values.

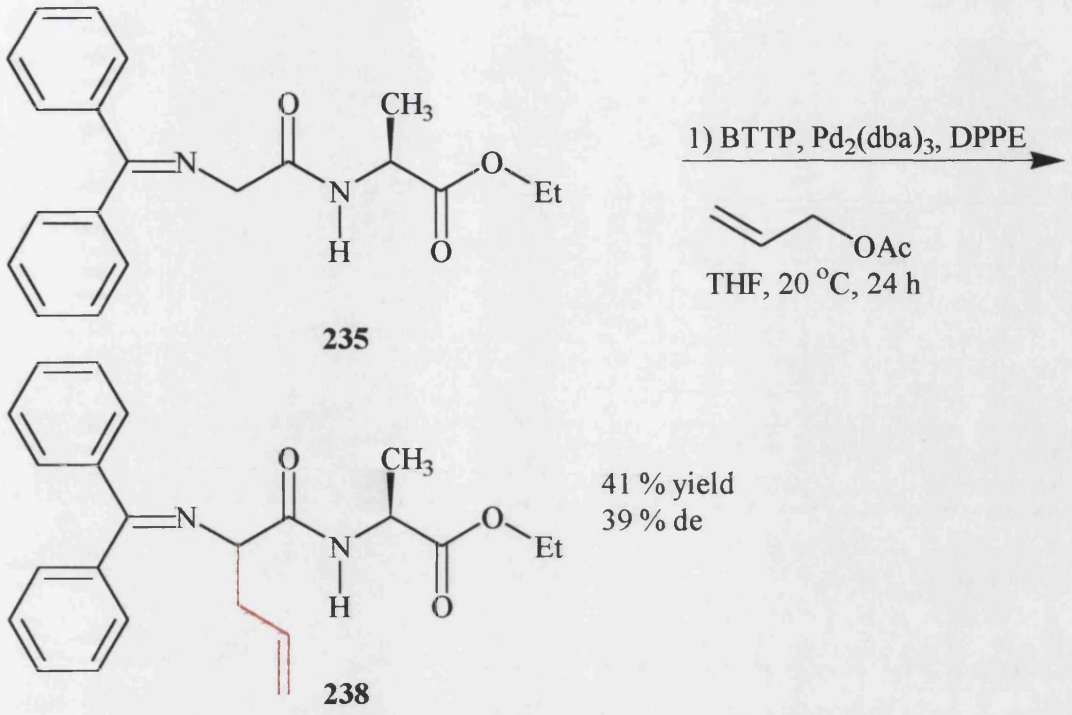
The reaction for *N*-(diphenyl methylene)-gly-L-phe-OEt **236** went well affording colourless crystals in 73 % yield. The ^{1}H and ^{13}C NMR spectrum were satisfactory with the

characteristic CH_2=N singlet appearing at 3.96 and 61.2 ppm respectively and the side chain CH_2 appearing at 3.2 and 37.9 ppm respectively. The signals relating to the phenyl group appeared at 7.1-7.8 ppm and at 126.9-135.7 ppm in the ^1H and ^{13}C NMR spectrum respectively. The accurate mass and CHN were satisfactory (M^+ 380.2100 was found, $C_{23}H_{28}N_2O_3$ requires M^+ 380.2099), (C 72.5 %, H 7.38 %, N 7.26 % $C_{23}H_{28}N_2O_3$ requires C 72.5%, H 7.41% and N 7.36%).

The reaction for *N*-(diphenyl methylene)-gly-L-leu-OEt compound **237** went well affording colourless crystals in 57 % yield. The ^1H and ^{13} C NMR spectrum were satisfactory with the characteristic CH_2=N singlet appearing at 4.0 ppm and 56.2 ppm, and the side chain CH and CH_2 peaks appearing between 1.64 ppm and 1.74 ppm, and at 22.8 ppm and 25.0 ppm. The values for the methyl groups' peaks were 0.99 ppm for the ^1H NMR spectrum, and 22.1 ppm and 22.8 ppm for the ^{13} C NMR spectrum . In addition an x-ray of this structure was obtained.

(xxviii) Investigation of the neighbouring amino acid effect in solution phase chemistry

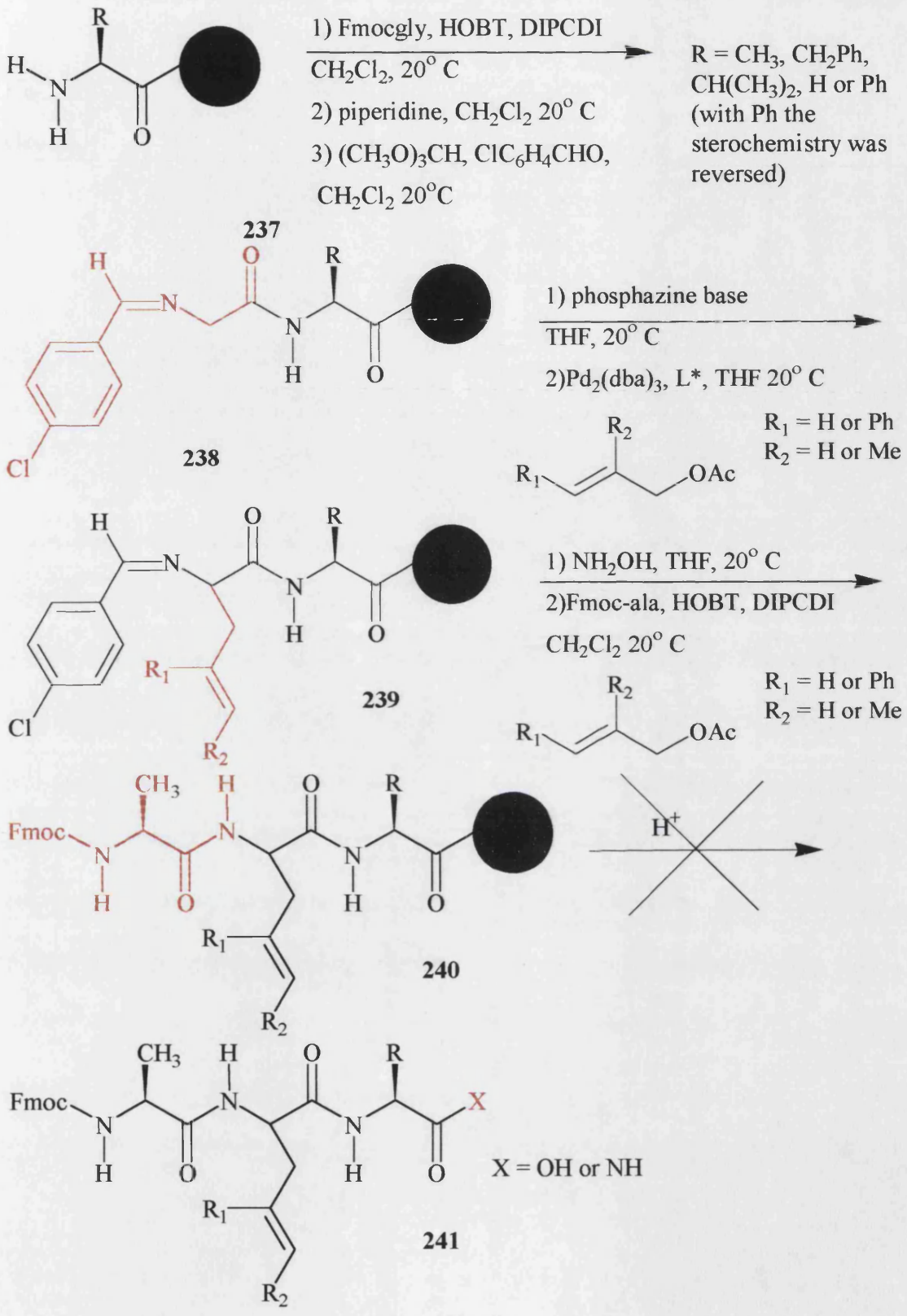
Unfortunately only the allylation of *N*-(diphenyl methylene)-gly-L-ala-OH **235** was successful (Scheme 81). The product was characterised by ^{13}C and ^1H NMR spectrum . The singlet at 4 ppm in ^1H NMR spectrum **235** disappeared. and the CH_2 in the DEPT ^{13}C NMR spectrum at 61.3 ppm was replaced by a CH signal at 65.4ppm. The de of the product was 39 %. This was calculated by irradiating at 4.2 & 4.6 ppm in the ^1H NMR spectrum and decoupling the methyl signals. The integration of the methyl signals in the two diastereomers was then compared to give the de. The accurate mass was satisfactory (M^+ 379.2021, $C_{23}H_{27}N_2O_3$ requires M^+ 379.2021). The reactions with the other substrates gave unreacted starting material. This was because this type of reaction is very temperamental; although a great deal of care was taken it rarely gave the same results twice in a row.



Scheme 81

(xxix) Investigation of the scope of the reaction

An extensive screening programme was then carried out to see the effects of the neighbouring amino acid, ligand and solvent on the de in solid phase chemistry. (Scheme 82). After allylation had taken place the imine was removed and alanine coupled onto the chain. For allyl-gly-gly-OH this means that the stereochemistry induced by the ligand can be seen by NMR spectrum as it is now de instead of ee. However despite a large amount of effort, the experiments were not successful. The scheme of the attempted reactions is shown on the next page.


1) Fmocgly, HOBT, DIPCDI
CH_2Cl_2, 20° C
2) piperidine, CH_2Cl_2 20° C
3) $(CH_3O)_3CH$, ClC_6H_4CHO,
CH_2Cl_2 20°C
R = CH_3, CH_2Ph, $CH(CH_3)_2$, H or Ph (with Ph the sterochemistry was reversed)
237
238
1) phosphazine base
THF, 20° C
2)$Pd_2(dba)_3$, L*, THF 20° C
R_1 = H or Ph
R_2 = H or Me
OAc
239
1) NH_2OH, THF, 20° C
2)Fmoc-ala, HOBT, DIPCDI
CH_2Cl_2 20° C
240
241
X = OH or NH

Scheme 82

After carrying out these reactions scheme, unallylated tripeptide was the only product. Unfortunately it was not possible to see if the allylation had gone to completion prior to cleavage.

(xxx) Conclusion

Glycine equivalents in dipeptides in both solution and solid phase have been allylated using palladium methodology. This was despite the difficulties outlined above. The main problem with this methodology is that it does not always allylate the glycine equivalent to afford the desired product. This difficulty persisted despite altering many factors, such as solvent, base and imine and always taking care to exclude moisture and air from the reaction conditions. As a result it was not possible to investigate fully the scope of the methodology both with respect to the range of electrophiles that could be used and the most effective ligands for inducing chirality in the substituted glycine.

A possible reason for the methodology not being consistently reproducible which I have discovered since finishing the practical aspects of my research is that moisture may have been trapped in the resin. A Karl Fisher analysis of the resin to find the water content, prior to the palladium catalysed allylation, would have indicated if this was the case. If the water content had been high, azetrope drying with toluene would have removed the water and hopefully solved the problem. However over-drying of resin can result in a loss of resin structure making it difficult to re-swell the resin later, which would replace one problem with another.[98] If the resin could not be swollen sufficiently the reactants would be unable to penetrate its matrix and therefore to come into contact with the peptide chains.

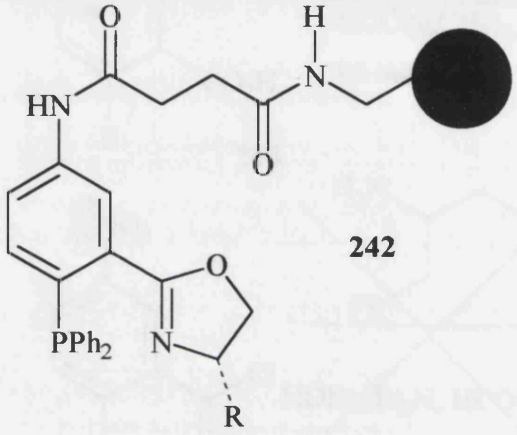
Another possible solution to the trapped moisture problem (if it was the problem), would be to run the reaction in the presence of a dehydrating agent.

Chapter 4

Attempts to synthesise oxazoline ligands attached to resin

(i) Proposed structure of the ligand

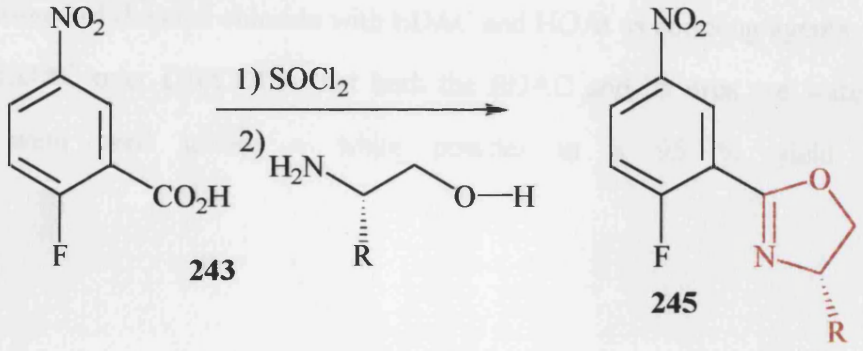
Oxazoline ligands have been used in palladium catalysed allylation for many years.[50,51&52] During part of our research we attempted to synthesise an oxazoline ligand attached to a resin. The structure of the ligand was to be :-



242

(ii) Proposed route of synthesis

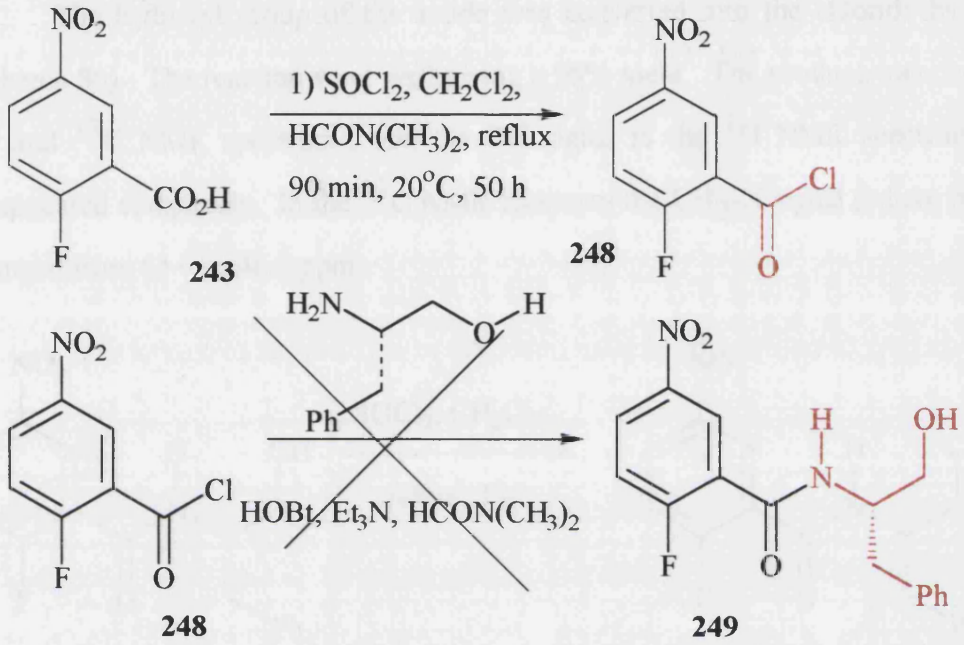
The proposed route for the synthesis was an adaptation of Helmchen's method for the synthesis of oxazolines (Scheme 83).[51]:-



Scheme 83

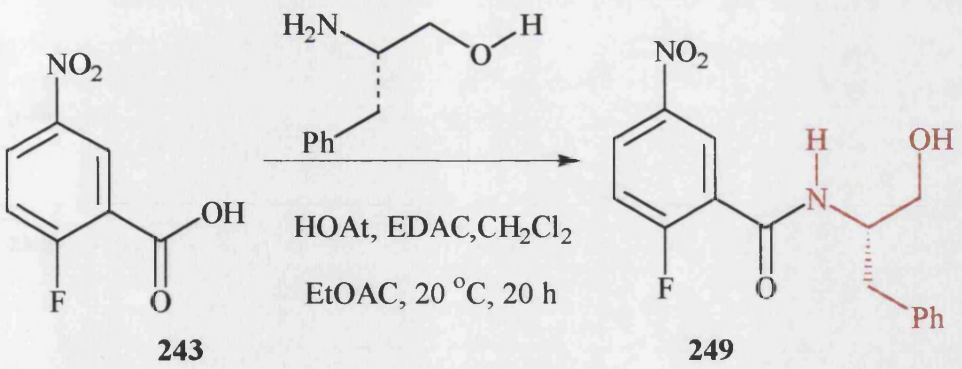
(iii) Attempted synthesis of oxazoline

The synthesis of the acid chloride using phenyl alaninol went smoothly and was monitored by IR which showed the frequency of the C=O bond stretch change from 1700 to 1760 cm^{-1}. The acid chloride was then used to make the amide (Scheme 84) without further characterisation.



Scheme 84

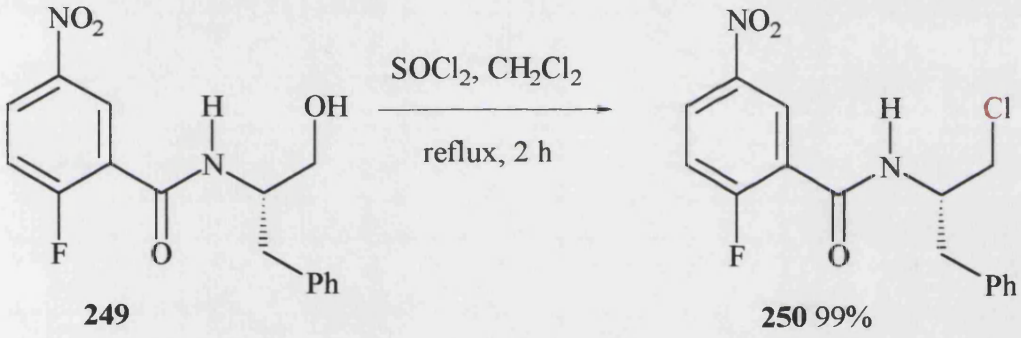
The synthesis of the amide using the above route, however, gave a mixture of compounds. It was therefore decided to try synthesising the amide by a different route, using the acid instead of the acid chloride with EDAC and HOAt as coupling agents. The advantage of using EDAC over DIPCDI is that both the EDAC and its urea are water soluble. The reaction went well giving a white powder in a 95 % yield (Scheme 85).



243 **249**

Scheme 85

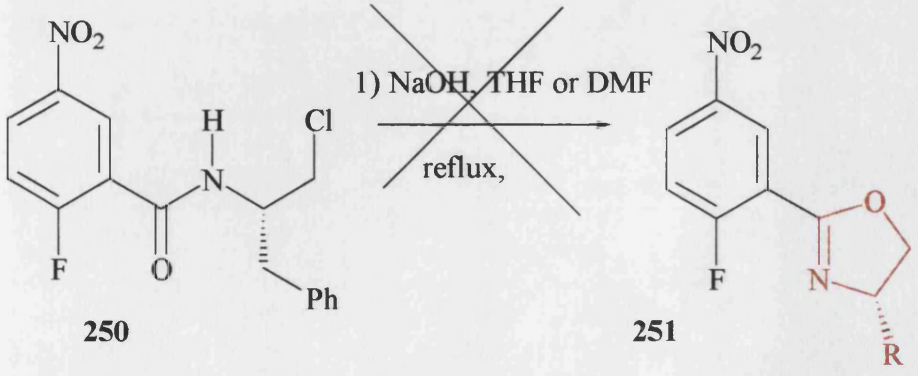
The hydroxyl group of the amide was converted into the chloride by using $SOCl_2$ (Scheme 86). The reaction went well giving a 99% yield. The product was characterised by ^1H and ^{13}C NMR spectrum , and the OH signal in the ^1H NMR spectrum at 2.1 ppm disappeared completely. In the ^{13}C NMR spectrum the CH_2-X signal (where X = OH or Cl) changed from 64.0 to 46.6 ppm.



249 **250** 99%

Scheme 86

The cyclisation with NaOH, however, was not so successful because it gave a mixture of products which could not be separated (Scheme 87).

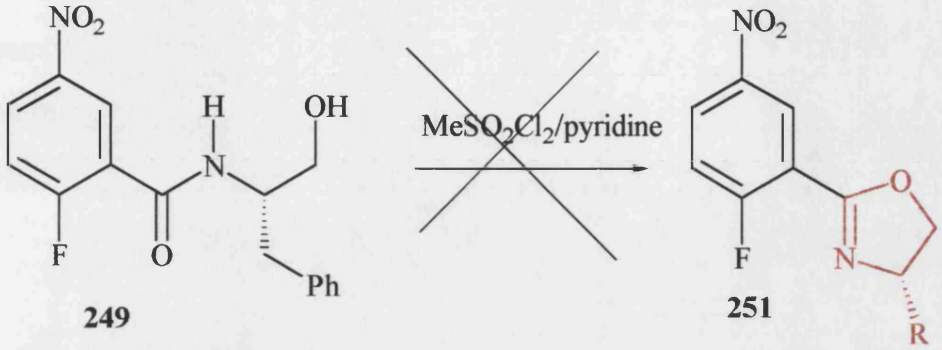


250 **251**

Scheme 87

The reason for this failure was thought to be due to the anion reacting with the fluorine attached to the phenyl ring as well as with the chloride.

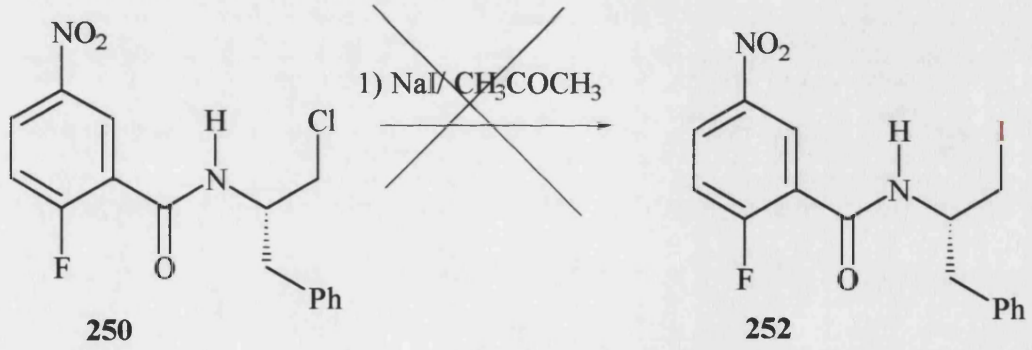
Various attempts were made to achieve this cyclisation. These included using KO^tBu as a base, using $MeSO_2Cl_2$/pyridine with the alcohol to achieve cyclisation (Scheme 88).



249 **251**

Scheme 88

In addition to the above an attempt was made to synthesise the iodide from the chloride (Scheme 89) in order to see if that would cyclise better. However after heating for six days at reflux in acetone the chloride remained unchanged.



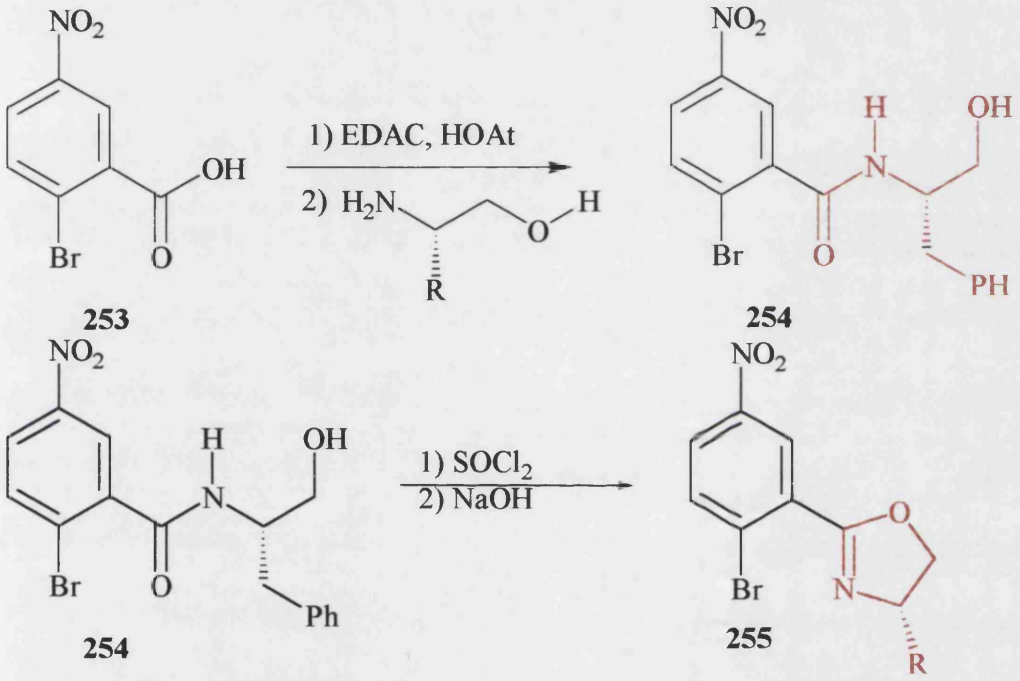
250 **252**

Scheme 89

After several unsuccessful attempts, we reluctantly abandoned this area of research.

(iv) CONCLUSION

Although this area of research did not fully achieve our aims, it was not entirely unprofitable. Oxazoline ligands are extensively used in palladium chemistry, and the synthesis of them attached to a solid support could be very useful. There are several possible synthetic routes to form these ligands. The benefit of our research is that we have now narrowed the number of these possible routes, which would be worth pursuing in the future. If we had had more time we would have tried the synthesis again using the alternative route below (Scheme 90).



Scheme 90

Chapter 5

Experimental

Solvents and reagents - Commercially available solvents and reagents were used throughout without further purification, except for those detailed below which were purified as described. Petroleum ether refers to petroleum with a boiling point between 40-60 °C. Dichloromethane was dried by distilling over $CaSO_4$ prior to use, THF was distilled over sodium benzophenone ketyl. TGR resin was supplied by British Biotech as the Fmoc protected form and was deprotected by shaking with 20% piperidine in CH_2Cl_2 or DMF for 1 hour prior to use.

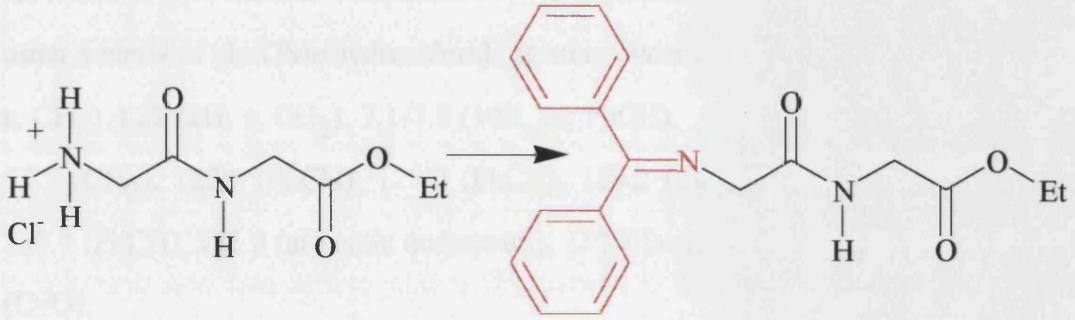
Chromatographic Procedures - Analytical thin layer was carried out using plastic backed plates coated with Merck Kieselgel 60 F_{254}. Plates were visualised under UV light (at 254 and / or 360 nm) or by staining with potassium permanganate solution or ninhydrin followed by heating. "Flash" chromatography was carried out using Merck silica gel 60. Pressure was applied at the head of the column with hand bellows. Samples were applied either pre-absorbed on silica or as a concentrated solution in an appropriate solvent. Columns were collected and monitored by thin layer chromatography.

Spectroscopic Techniques - Infra red spectra were recorded in the range 4000-600 cm^{-1} using a Nicolet FT-205 and a Perkin Elmer 1600 series FT-IR spectrophotometer with internal calibration. Spectra were recorded as thin films. ^1H and ^{13}C NMR spectrum were performed on Jeol JNM- GX 270 machines. NMR spectrum spectra were referenced against tetramethylsilane except in the case of D_2O when they were referenced against residual undeutrated solvent. Signals are described as singlets (s), doublets (d), multiplets (m) etc. Elemental analyses were performed on a Carlo Erba 1106 Elemental Analyser.
Melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected. High and low resolution mass spectra were recorded on a Kratos MS80 instrument and the Micromass Autospec.

All palladium allylation reactions were performed under Ar or N_2 using standard techniques. Prior to both palladium allylation and cleavage the resin was dried in a vacuum oven overnight.

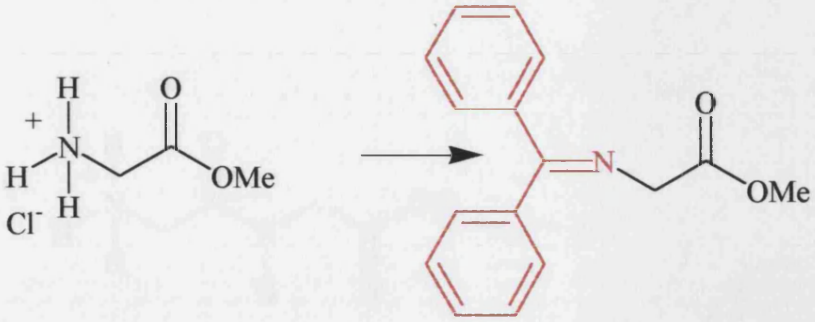
(i) Preparation of imines

***N*-(diphenyl methylene)-gly-gly-OEt 119**



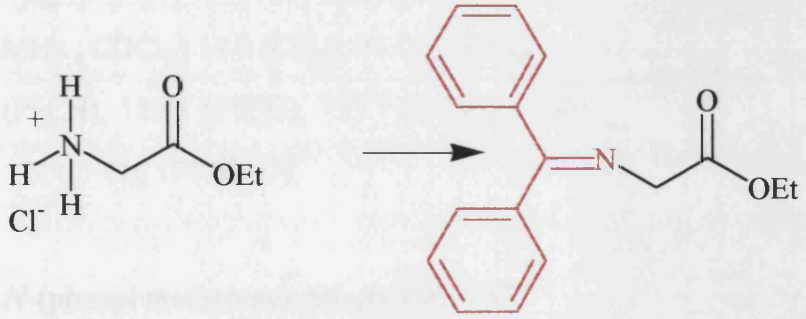
gly-gly-OEt HCl (5.00 g, 25.43 mmol, 1.1 equivalents) and benzophenone imine (3.9 ml, 23.30 mmol, 1 equivalent), were stirred together in CH_2Cl_2 (200 ml) for 24 h. The solvent was removed *in vacuo* and the solid remaining dissolved in EtOAc. It was washed (H_2O (100ml x 2)), ($NaHCO_{3\ (aq)}$ (sat.) (100 ml x 1)), (H_2O (50 ml x 1)), dried ($MgSO_4$), the solvent was removed *in vacuo* to give the *title compound* **119** as a colourless solid (6.754 g, 20 mmol, 86 %). M.p. 122-123 °C (Found: $M+1^+$ 325.1553, $C_{19}H_{20}N_2O_3$ requires M^+324.1473). ν_{max}/cm^{-1} (neat) 1741 (CO_2Et), 1623 (C=N), and 1541 (N-H). δ_H (270 MHz ; $CDCl_3$), 1.3 (3H, t, ***J*** 7.1, CH_3), 4.0 (2H, s, $C\underline{H}_2CONH$), 4.16 (2H, d, ***J*** 5.8, $C\underline{H}_2$), 4.27 (2H, q, ***J*** 7.1, $C\underline{H}_2CO$), 7.1-7.8 (10H, m, PhC<u>H</u>), 8.10 (1H, s, NH). δ_C (67.5 MHz ; $CDCl_3$) 14.1 (CH_3), 41.0 ($\underline{C}H_2CO_2$), 56.4 ($\underline{C}H_2CH_3$), 61.4 ($\underline{C}H_2CONH$), 127.1 (Ph<u>C</u>H), 128.1 (Ph<u>C</u>H), 128.4 (Ph<u>C</u>H), 128.8 (Ph<u>C</u>H), 128.9 (Ph<u>C</u>H), 130.6 (Ph<u>C</u>H), 136 (C-quaternary aromatic), 138 (C-quaternary aromatic), 170 (C=N), 172 (C=O), 174 (C=O).

***N*-(diphenyl methylene)-gly-OMe 97**



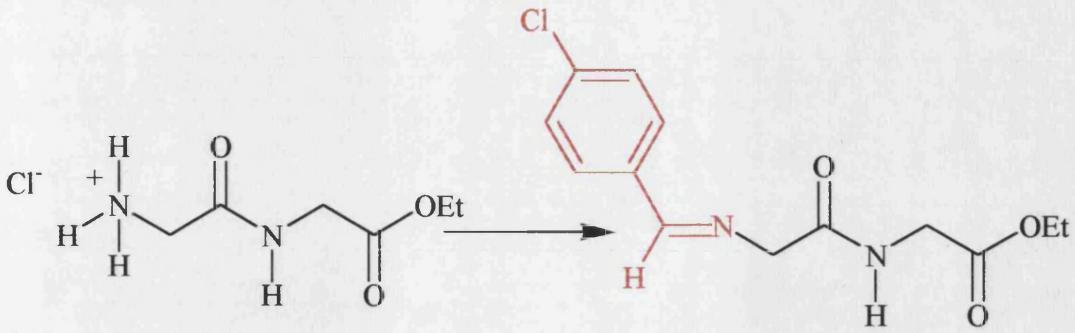
As above to give the *title compound* **97**[74] as a colourless oil in (0.411 g, 54 %, 1.62 mmol) using 3 mmol of gly-OMe hydrochloride starting material. δ_H (270 MHz ; $CDCl_3$), 3.74 (3H, s, CH_3) 4.22 (2H, s, CH_2), 7.1-7.8 (10H, m, PhC<u>H</u>). δ_C (67.5 MHz ; $CDCl_3$) 51.7 (CH_3), 55.5 (CH_2), 127.6 (Ph<u>C</u>H), 128.0 (Ph<u>C</u>H), 128.2 (Ph<u>C</u>H), 128.6 (Ph<u>C</u>H), 128.7 (Ph<u>C</u>H), 130.4 (Ph<u>C</u>H), 135.9 (aromatic quaternary), 139.2 (aromatic quaternary), 171.1 (C=N), 171.8 (C=O).

***N*-(diphenyl methylene)-gly-OEt 112**



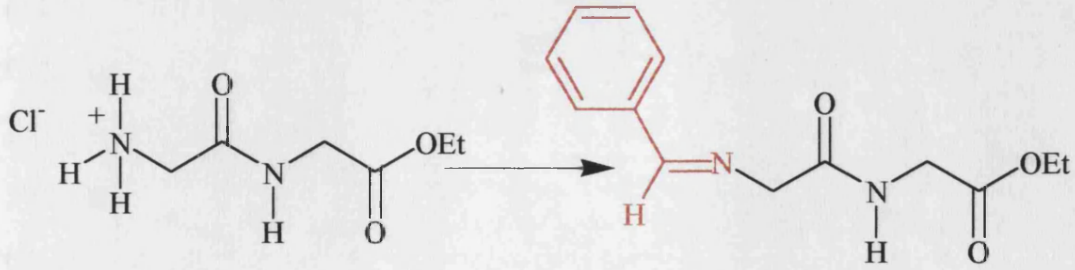
As above to give the *title compound* **112** as a colourless solid in (4.27 g, 80 %, 16 mmol) using 20 mmol of gly-OEt hydrochloride starting material. δ_H (270 MHz ; $CDCl_3$) 1.24 (3H, t, ***J*** 7.1, CH_3), 4.22 (4H, m, CH_2CO_2 & CH_2CH_3), 7.1-7.8 (10H, m, PhC<u>H</u>). δ_C (67.5 MHz) 14.2 (CH_3), 55.7 (OCH_2), 60 (CH_2), 127.6 (Ph<u>C</u>H), 128.0 (Ph<u>C</u>H), 128.6 (Ph<u>C</u>H), 128.8 (Ph<u>C</u>H), 128.7 (Ph<u>C</u>H), 130.4 (Ph<u>C</u>H), 135 (aromatic quaternary), 139 (aromatic quaternary), 171. (C=N), 173 (C=O).

***N*-(*p*-chloro phenyl methylene)-gly-gly-OEt 127**



gly-gly-OEt HCl (465 mg, 2.4 mmol, 1.2 equivalents), *p*-chloro benzaldehyde (281 mg, 1.99 mmol, 1 equivalent), triethylamine (0.34 ml, 2.4 mmol, 1.2 equivalents) and trimethyl orthoformate (0.6 ml, 5.5 mmol, 2.5 equivalents) were stirred together in CH_2Cl_2 (200 ml) for 60 h. The solution was washed (H_2O (50 ml x 1)), dried ($MgSO_4$), the solvent was removed *in vacuo* to give the *title compound* **127** as a colourless solid (523 mg, 1.75 mmol, 88 %). M.p. 88-89 °C % (Found: $M+1^+$, 283.0842 $C_{13}H_{15}N_2O_3Cl$ requires M^+ 282.0771). ν_{max}/cm^{-1} (neat) 1743 (C=O), 1668 (C=N), and 1527 (N-H). δ_H (270 MHz ; $CDCl_3$), 1.26 (3H, t, *J* 7.4, CH_3), 4.1 (2H, d, *J* 5.3, $C\underline{H}_2CO_2$), 4.21 (2H, q, J 7.1, $C\underline{H}_2CH_3$), 4.31 (2H, s, $C\underline{H}_2CONH$), 7.1-7.8 (10H, m, PhC<u>H</u>), 8.08 (1H, s, NH) 8.3 (1H, s, HPhC=N). δ_C (67.5 MHz ; $CDCl_3$) 14.0 (CH_3), 41.0 ($\underline{C}H_2CO_2$), 61.4 ($\underline{C}H_2CONH$), 62.3 ($CO_2\underline{C}H_2CH_3$), 128.9 (Ph<u>C</u>H), 129.4 (Ph<u>C</u>H), 133.7 (aromatic quaternary), 137.3 (aromatic C-Cl), 162.3 (C=N), 172 (C=O), 174 (C=O).

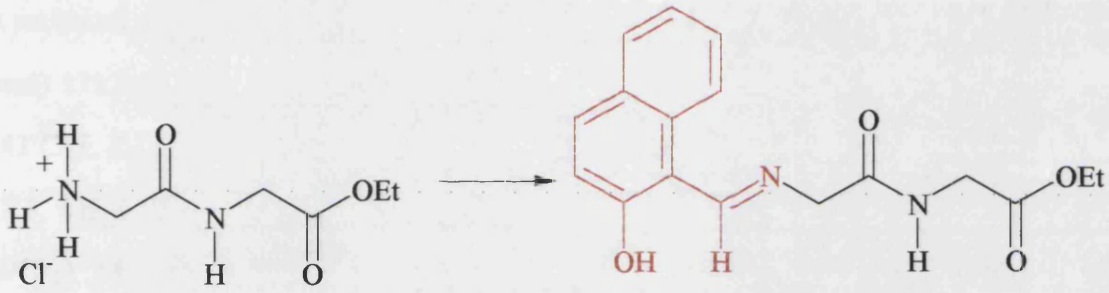
***N*-(phenyl methylene)-gly-gly-OEt 128**



gly-gly-OEt HCl (435 mg, 2.2 mmol, 1.1 equivalents), benzaldehyde (0.2 ml, 1.99 mmol, 1 equivalent), triethylamine (0.34 ml, 2.4 mmol, 1.2 equivalents), and trimethyl orthoformate

(0.6 ml, 5.5 mmol, 2.5 equivalents) were stirred together in CH_2Cl_2 (200 ml) for 60 h. The solution was washed (H_2O (50 ml x 1)), dried ($MgSO_4$) and the solvent was removed *in vacuo* to give the *title compound* **128** as a colourless oil (298 mg, 1.2 mmol, 60 %). (Found M^+ 249.1240 $C_{13}H_{16}N_2O_3$ requires M^+ 249.1239). ν_{max}/cm^{-1} (neat) 1745 (CO_2Et), 1650 (C=N), and 1526 (N-H). δ_H (270 MHz ; $CDCl_3$), 1.3 (3H, t, ***J*** 6.6, CH_3), 4.10 (2H, d, ***J*** 5.3, $C\underline{H}_2CO_2$), 4.21 (2H, q, ***J*** 7.1, $C\underline{H}_2CH_3$), 4.31 (2H, s, $C\underline{H}_2CONH$), 7.1-7.8 (10H, m, PhC<u>H</u>), 8.07 (1H, s, NH), 8.3 (1H, s, HPhCN). δ_C (67.5 MHz ; $CDCl_3$) 14.1 (CH_3), 40.0 ($\underline{C}H_2CO_2$), 61.4 ($\underline{C}H_2CONH$), 62.4 ($CO_2\underline{C}H_2CH_3$), 128.1 (Ph<u>C</u>H), 129.1 (Ph<u>C</u>H), 131.4 (Ph<u>C</u>H), 132.8 (Ph<u>C</u>H), 135 (aromatic quaternary), 163 (C=N), 169 (C=O), 170 (C=O) .

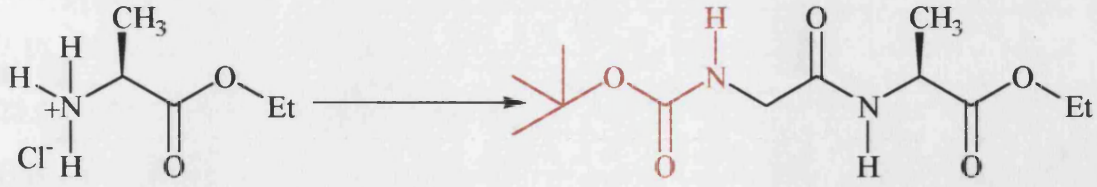
_N_-(2-Hydroxy-1-naphathal)-gly-gly-OEt 131



gly-gly-OEt HCl (1.966 g, 10 mmol, 1 equivalent), 2-hydroxy-1-napthaldehyde (2.58 g, 15 mmol, 1.5 equivalents) and triethylamine (1.01g, 10 mmol, 1 equivalent) were stirred together in CH_3OH (200 ml) for 24 h. The solvent was then removed *in vacuo* and the solid washed with Et_2O to give the *title compound* **131** as a yellow solid (2.906g, 9.26 mmol, 92.6 %). ν_{max}/cm^{-1} (neat) 3325 (OH), 1739 (C=O), 1667 (C=N), and 1541 (N-H). δ_H (270 MHz ; $(CD_3)_2SO$), 1.8 (3H, t, ***J*** 7.1, CH_3), 4.0 (2H, d, ***J*** 5.3, $C\underline{H}_2CO_2$), 4.2 (2H, q, ***J*** 7.1, $C\underline{H}_2CH_3$), 4.4 (2H, s, $C\underline{H}_2CONH$), 6.9-7.7 (8H, m, PhC<u>H</u>), 8.7 (1H, s, OH), 9.1 (1H, d, ***J*** 11.3, NH), 13.6 (1H, s, COH). δ_C (67.5 MHz ; $(CD_3)_2SO$) 17.1 (CH_3), 40.0 ($\underline{C}H_2CO_2$), 56.4 ($\underline{C}H_2CONH$), 60.4 ($\underline{C}H_2CH3$), 118 (Ar<u>C</u>H), 123.1 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 130.8 (aromatic quaternary), 136.4 (aromatic quaternary), 138 (aromatic quaternary), 163.5 (C-OH), 169.2 (C=N), 171.3 (C=O), 176.4 (C=O)

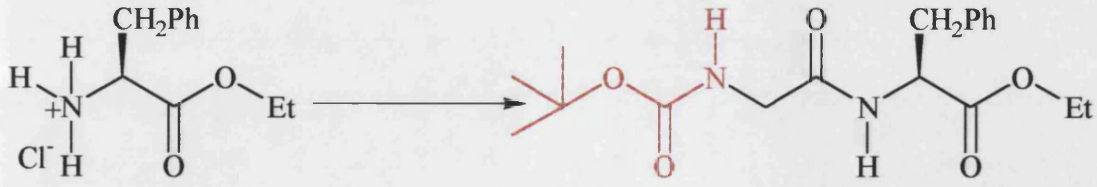
(ii) Preparation of dipeptides

^{t}Boc-gly-L-ala-OEt 230



^{t}Boc-gly-N-hydroxysuccinimide (1.033g, 4.03 mmol, 1 equivalent) , L-ala-OEt (0.618g, 4.03 mmol, 1 equivalent) and triethylamine (0.7 ml, 5 mmol, 1.25 equivalent) were stirred together in MeCN (24 ml) and H_2O (12 ml), for 24 h. The solvent was then removed *in vacuo* and the solid remaining dissolved in EtOAc (200 ml). It was washed ($NH_4Cl_{(aq)}$ (sat) 50ml x 1), ($NaHCO_{3\ (aq)}$ (sat.) 50 ml x 1), (H_2O (50 ml x 1), dried ($MgSO_4$) , the solvent was removed *in vacuo* to give the *title compound* **230** as a oil (943 mg, 3.44 mmol, 85 %). ν_{max}/cm^{-1} (neat) 1712 (C=O) and 1529 (C=N). δ_H (270 MHz ; $CDCl_3$), 1.26 (3H, t, ***J*** 7.1, $CH_2\underline{C}H_3$), 1.41 (3H, ***J*** 12.1, $CH\underline{C}H_3$) 1.44 (9H, s, $C(CH_3)_3$), 3.83 (2H, m, $\underline{C}H_2CONH$), 4.1-4.2 (2H, q, ***J*** 7.1, $C\underline{H}_2CH_3$), 4.6 (1H, m, $\underline{C}HCO_2$), 5.1 (1H, bs, NH), 6.7 (1H, bs, NH). δ_C (67.5 MHz ; $CDCl_3$) 14.1 (CH_3), 18.6 (CH_3), 25.6 (CH_3), 44.7 ($\underline{C}H_2CH_3$), 52.3 ($\underline{C}HCO_2$), 61.8 ($\underline{C}H_2CONH$), 80.7 ($\underline{C}(CH_3)_3$), 156 (C=O), 169 (CONH), 174 (C=O).

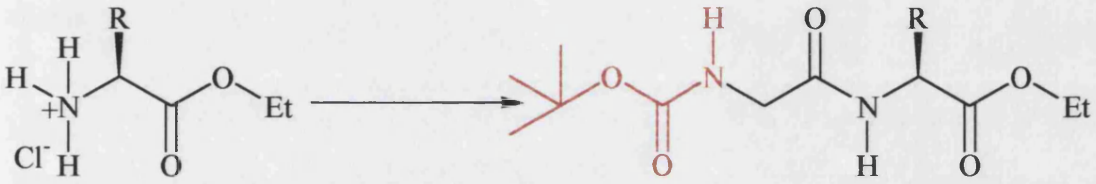
^{t}Boc-gly-L-phe-OEt 231



^{t}Boc-gly-N-hydroxysuccinimide (1.09g, 4.28 mmol, 1 equivalent), L-phe-OEt (0.982g, 4.28 mmol, 1 equivalent) and Et_3N (0.7 ml, 5 mmol, 1.25 equivalent) were stirred together in MeCN (24 ml), H_2O (12 ml), for 24 h. The solvent was then removed *in vacuo* and the solid remaining dissolved in EtOAc (200 ml). It was washed ($NH_4Cl_{(aq)}$ (sat) 50ml x 1), ($NaHCO_{3\ (aq)}$ (sat.) (50 ml x 1)), (H_2O (50 ml x 1)), dried ($MgSO_4$) , the solvent was

removed in vacuo to give the *title compound* **231** as a colourless oil (1.02 g, 2.95 mmol, 70 %). ν_{max}/cm^{-1} (neat) 1720 (C=O) and 1531 (C=O). δ_H (270 MHz ; $CDCl_3$), 1.22 (3H, t, ***J*** 7.15, CH_3), 1.44 (9H, s, $C(CH_3)_3$), 3.1 (2H, d, ***J*** 6.0, $C\underline{H}_2Ph$), 3.75 (2H, m, $C\underline{H}_2CONH$), 4.10 (2H, q, ***J*** 7.1, $C\underline{H}_2CH_3$), 4.81 (1H, m, $C\underline{H}CO_2$), 5.23 (1H, bs, NH), 6.7 (1H, bs, NH) 7.10-7.13 (2H, m, PhC<u>H</u>), 7.22-7.31 (3H, m, PhC<u>H</u>). δ_C (100 MHz ; $CDCl_3$) 14.3 (CH_3), 25.6 (CH_3), 38.2 (CH_2Ph), 44.1 ($\underline{C}H_2CONH$), 53.9 ($\underline{C}HCO_2$), 80.3 ($\underline{C}(CH_3)_3$), 127.3 (Ph<u>C</u>H), 128.8 (Ph<u>C</u>H), 129.5 (Ph<u>C</u>H), 136.0 (aromatic quaternary), 156.2 (C=O), 169.4 (CONH), 171.6 (C=O).

^{t}Boc-gly-L-leu-OEt 232

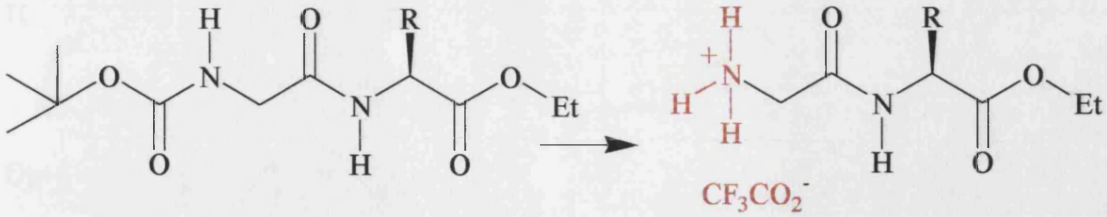


R = $CH_2CH(CH_3)_2$

^{t}Boc-gly-N-hydroxysuccinimide (2.1g, 7.72 mmol 1 equivalent), L-leu-OEt (1.51g, 7.72 mmol, 1 equivalent) and triethylamine (1.2 ml, 8.6 mmol, 1.1 equivalent) were stirred together in MeCN (24 ml), H_2O (12 ml), for 24 h. The solvent was then removed *in vacuo* and the solid remaining dissolved in EtOAc (200 ml). It was washed ($NH_4Cl_{(aq)}$ (sat) 50ml x 1), ($NaHCO_{3\ (aq)}$ (sat.) (50 ml x 1)), (H_2O (50 ml x 1)), dried ($MgSO_4$) , the solvent was removed *in vacuo* to give the *title compound* **232** as a colourless oil (2.4 g, 7.6 mmol, 98.5 %). δ_H (270 MHz ; $CDCl_3$) 0.93 (6H, d, ***J*** 5.2, CH_3), 1.22 (3H, t, ***J*** 7.15, CH_3), 1.44 (9H, s, $C(CH_3)_3$), 1.7 (2H, m, $C\underline{H}_2(CH_3)_2$), 3.8 (2H, m, $C\underline{H}_2CONH$), 4.1 (2H, q, ***J*** 7.1, $C\underline{H}_2CH_3$), 4.6 (1H, m, $CHCO_2$), 5.2 (1H, bs, NH), 6.6 (1H, bs, NH). δ_C (100 MHz ; $CDCl_3$) 13.9 (CH_3), 20.2 (CH_3), 22.6 (CH_3), 24.5 ($\underline{C}H(CH_3)_2$), 43.9 (CH_2), 45.3 ($\underline{C}H_2CONH$), 50.5 ($\underline{C}HCO_2$), 61.9 ($\underline{C}H_2CH_3$), 80.6 ($\underline{C}(CH_3)_3$), 156.2 (C=O), 169.4 (CONH), 171.6 (C=O)

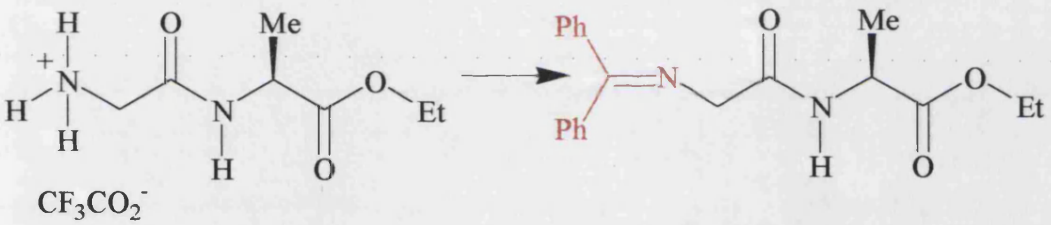
(iii) Deprotection of dipetides

General procedure for deprotection of ^{t}Boc dipeptide ethyl esters



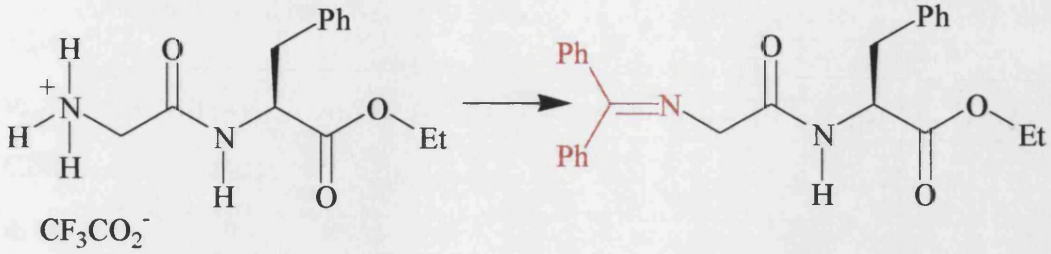
^{t}Boc-gly-Lala-OEt (0.943g, 3.44 mmol 1 equivalent) was stirred in a mixture of CH_2Cl_2 (4.5 ml) and CF_3CO_2H (1.5 ml), for 24 h. It was removed *in vacuo* with toluene to give an oil (837 mg, 2.93 mmol, 85 %). This was then used without analysis for making the imines and a similar procedure was used for the other two dipeptides.

***N*-(diphenyl methylene)-gly-L-ala-OEt 235**



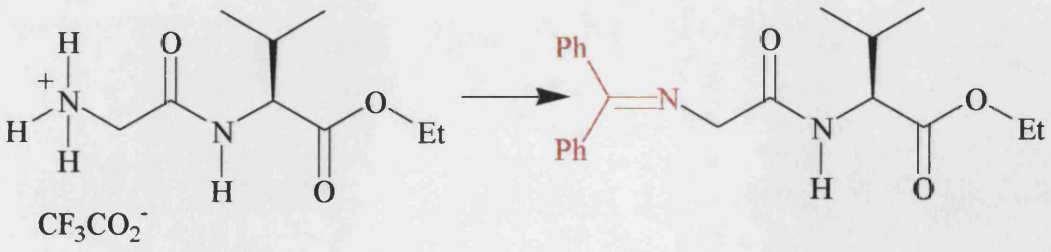
Gly-L-ala-OEt (crude product from deprotection 0.837g, 2.93 mmol, 1 equivalent), benzophenone imine (0.624 ml, 3.72 mmol, 1.25 equivalents), were stirred together in a mixture of CH_2Cl_2 (25 ml) with Et_3N (1.5 ml, 10.76 mmol, 3.67 equivalents) for 24 h. The solution was filtered through silica and the solvent removed *in vacuo* to give the *title compound* **235** as a colourless oil (691 mg, 2.0 mmol, 69 %). ν_{max}/cm^{-1} (neat) 1736 (C=O) and 1664 (C=O). δ_H (270 MHz ; $CDCl_3$) 1.3 (3H, t, ***J*** 7.1, CH_3), 1.4 (3H, d, ***J*** 5.8, CH_3), 4.0 (2H, s, $C\underline{H}_2CONH$), 4.16 (2H, d, ***J*** 5.8, $C\underline{H}_2CH_3$), 4.2 (2H, q, ***J*** 7.1, $C\underline{H}_2CO$), 4.7 (1H, q, $C\underline{H}CH_3$), 7.1-7.8 (10H, m, PhC$\underline{H}$), 8.1 (1H, s, NH). δ_C (67.5 MHz: $CDCl_3$) 14.0 (CH_3), 18.6 (CH_3), 47.7 ($\underline{C}HCO_2$), 56.4 ($\underline{C}H_2CH_3$), 61.3 ($\underline{C}H_2CONH$), 127.2 (Ph$\underline{C}$H), 128.2 (Ph$\underline{C}$H), 128.2 (Ph$\underline{C}$H), 128.3 (Ph$\underline{C}$H), 128.8 (Ph$\underline{C}$H), 128.9 (Ph$\underline{C}$H), 130.2 (Ph$\underline{C}$H), 130.6 (Ph$\underline{C}$H), 132.3 (Ph$\underline{C}$H), 170 (C=N), 172 (C=O), 174 (C=O).

_N_-(diphenyl methylene)-gly-L-phe-OEt 236



Gly-L-phe-OEt (crude product from deprotection, 6.8 mmol, 1 equivalent), benzophenone imine (1.14 ml, 6.8 mmol, 1 equivalent), triethylamine (3.4 ml, 24.4 mmol, 3.6 equivalent) were stirred in CH_2Cl_2 (70 ml) for 50 h. Purified as above to give the *title compound* **236** as colourless crystals 1.99 g (4.98 mmol, 73 %). M.p. 91.5-92.5 °C. (Found: $M+1^+$ 415.2026, $C_{26}H_{26}N_2O_3$ requires M^+ 414.1943), (Found: C 74.8 %, H 6.35 %, N 6.49 % $C_{26}H_{26}N_2O_3$ requires C 75.3 % , H 6.30 % and N 6.80 %). δ_H (270 MHz ; $CDCl_3$) 1.23 (3H, t, ***J*** 7.1, CH_3), 3.2 (2H, m, CH_2Ph), 3.96 (CH_2CONH), 4.20 (2H, q, ***J*** 7.1, CH_2CH_3), 4.95 (1H, m, $CHCO_2$), 7.1-7.8 (10H, m, PhCH), 8.1 (1H, NH, d, ***J*** 8.3). δ_C (67.5 MHz ; $CDCl_3$) 13.9 (CH_3), 37.9 (CH_2Ph), 52.5 ($CHCH_2Ph$), 56.2 (CO_2CH_2), 61.2 (CH_2CONH), 126.9 (PhCH), 127.0 (PhCH), 127.9 (PhCH), 128.1 (PhCH), 128.2 (PhCH), 128.3 (PhCH), 128.4 (PhCH), 128.6 (PhCH), 128.7 (PhCH), 129.2 (PhCH), 129.8 (PhCH), 130.0 (PhCH), 130.5 (PhCH), 132.2 (PhCH), 135.7 (PhCH), 137.4 (aromatic quaternary), 138.4 (aromatic quaternary), 169.9 (C=N), 170.2 (C=O), 171.1 (C=O).

_N_-(diphenyl methylene)-gly-L-leu-OEt 237

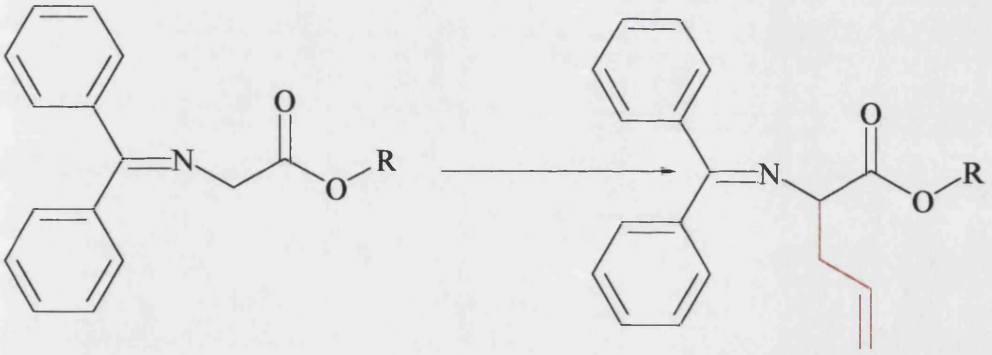


Gly-L-leu-OEt (crude product from deprotection, 8.31 mmol, 1 equivalent), benzophenone imine (1.40 ml, 8.31 mmol, 1 equivalent), triethylamine (4.0 ml, 28.7 mmol, 3.45 equivalent) were stirred in CH_2Cl_2 (100 ml) for 50 h. Purified as above, it was then recrystallised from

CH_2Cl_2/C_6H_{14} to give the *title compound* **237** as colourless crystals (1.173g, 4.7 mmol, 57 %). M.p. 76-77 °C (Found: M^+ 380.2100, $C_{23}H_{28}N_2O_3$ requires M^+ 380.2099), (Found C 72.5 %, H 7.38 %, N 7.26 % $C_{23}H_{28}N_2O_3$ requires C 72.5%, H 7.41% and N 7.36%). ν_{max}/cm^{-1} (neat) 1738 (C=O) and 1680 (C=O). δ_H (270 MHz ; $CDCl_3$), 0.99 (6H, d, ***J*** 5.3, CH_3),1.3 (3H, t, ***J*** 7.1, CH_3), 1.64-1.74 (3H, m, CH_2 and CH), 4.0 (2H, s, $C\underline{H}_2CONH$), 4.18, (2H, d, ***J*** 7.1, $C\underline{H}_2CH_3$), 4.7 (1H, m, $C\underline{H}CO_2$), 7.1-7.8 (10H, m, PhC<u>H</u>), 7.9 (1H, broad peak, NH). δ_C (100 MHz ; $CDCl_3$) 14.1 (CH_3), 22.1 (CH_3), 22.8 (CH_3), 25.0 ($\underline{C}H_2CH(CH_3)_2$), 41.5 ($\underline{C}H(CH_3)_2$), 50.5 ($\underline{C}HCO_2$), 56.2 ($\underline{C}H_2CONH$), 61.2 ($\underline{C}H_2CH_3$), 127.3 (Ph<u>C</u>H), 128.2 (Ph<u>C</u>H), 129.4 (Ph<u>C</u>H), 128.9 (Ph<u>C</u>H), 128.9 (Ph<u>C</u>H), 130.7 (Ph<u>C</u>H), 136.0 (aromatic quaternary), 138.7 (aromatic quaternary), 170.2 (C=N), 170.4 (CONH), 172.5 (C=O).

(iv) Allylation of imines

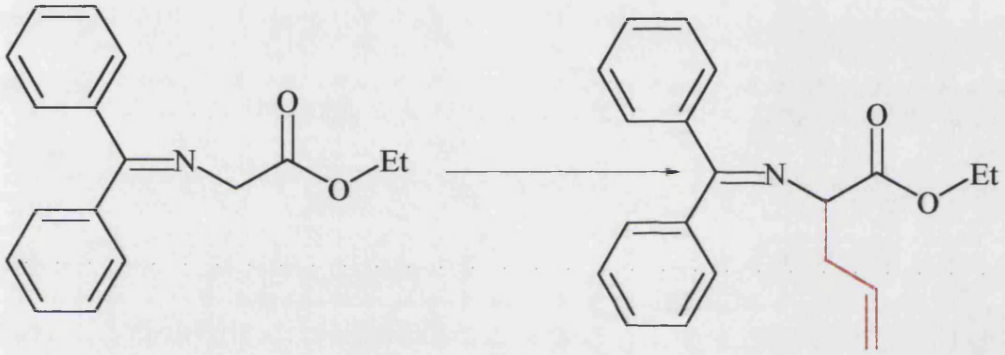
***N*-(diphenyl methylene)-allylgly-OMe 97**



Allyl palladium chloride dimer (9.8 mg, 0.026 mmol, 0.029 equivalents) and PPh_3 (52.4 mg, 0.2 mmol, 0.22 equivalents) were stirred together in THF (2 ml) for 10 min. Allyl acetate (0.14 ml, 1.5 mmol, 1.66 equivalents) was added and stirred for 10 min.. *N*-(diphenyl methylene)-gly-OMe (228 mg, 0.9 mmol, 1 equivalent), BSA (404 mg, 1.98 mmol 2.2 equivalents) and KOAc (5mg, 0.05 mmol, 0.055 equivalents) were stirred together in THF (2 ml) for 10 min. in a separate container. The Pd complex was added and stirred for 24 h. The solvent was removed and the compound was purified by "flash" column chromatography in

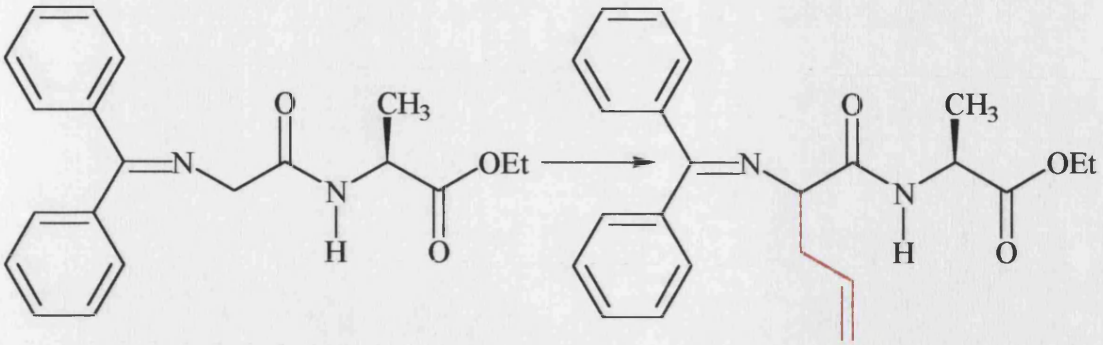
Et_2O: Petrol 1:4 to give the *title compound* **97**,[74] as a colourless oil (170 mg, 0.58 mmol, 64.5 %). ν_{max}/cm^{-1} (neat) 1739 (CO_2Me), 1660 (C=C), 1624 (C=N), and 1541 (N-H). δ_H (270 MHz ; $CDCl_3$), 2.64 (2H, m, $C\underline{H}_2CH$), 3.72 (3H, s, CH_3), 4.16 (1H, m, $CHCO_2$), 5.0 (2H, m, $C\underline{H}_2$=CH), 5.67 (1H, m, $C\underline{H}$=CH_2), 7.1-7.8 (10H, m, PhC$\underline{H}$). δ_C (67.5 MHz ; $CDCl_3$) 38.2 ($\underline{C}H_2CH$=CH_2), 52.0 (OCH_3), 65.2 ($\underline{C}HCO_2$), 117.4 ($\underline{C}H_2$=CH), 127.9 (Ph$\underline{C}$H), 128.0 (Ph$\underline{C}$H), 128.2 (Ph$\underline{C}$H), 128.4 (Ph$\underline{C}$H), 128.6 (Ph$\underline{C}$H), 128.8 (Ph$\underline{C}$H), 130.0 (Ph$\underline{C}$H), 132.3 (aromatic quaternary), 134.2 (aromatic quaternary), 136.7 ($\underline{C}H$=CH_2), 139.2 (aromatic quaternary), 172 (C=N), 174 (C=O).

_N_-(diphenyl methylene)-allylgly-OEt 115



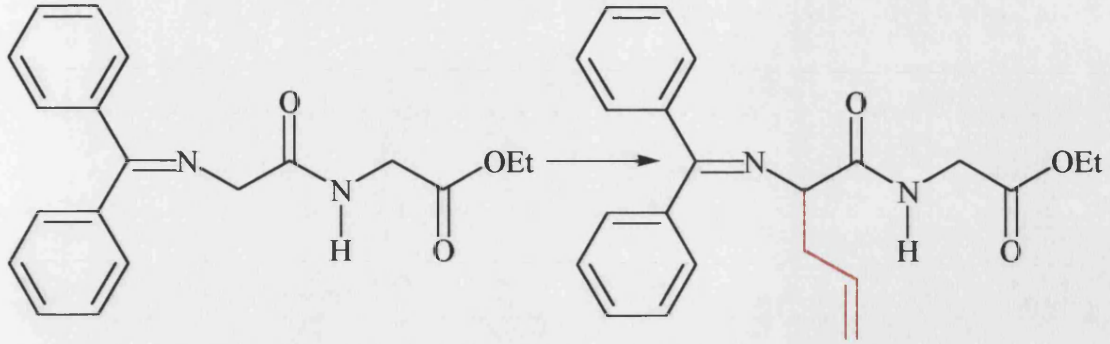
As above using petrol: EtOAc 5: 95 column eluent. To give the *title compound* **115** as a colourless oil (245 mg, 0.8 mmol, 80 %). δ_H (270 MHz ; $CDCl_3$), 1.26 (3H, t, ***J*** 7.7, CH_3), 2.63-2.67 (2H, m, $C\underline{H}_2CH$=CH_2), 4.11-4.23 (3H, m, $C\underline{H}$CONH & $C\underline{H}_2$CONH), 5.01-5.11 (2H, m, $C\underline{H}_2$=CH), 5.65-5.72 (1H, m, $C\underline{H}$=CH_2), 7.1-7.8 (10H, m, PhC$\underline{H}$). δ_C (63 MHz ; $CDCl_3$) 14.1 (CH_3), 38.1 ($\underline{C}H_2CH$=CH_2), 60.8 ($\underline{C}H_2CH_3$), 65.3 ($\underline{C}HCO_2$), 117.5 ($\underline{C}H_2$=CH), 127.9 (Ph$\underline{C}$H), 128.0 (Ph$\underline{C}$H), 128.2 (Ph$\underline{C}$H), 128.4 (Ph$\underline{C}$H), 128.6 (Ph$\underline{C}$H), 128.8 (Ph$\underline{C}$H), 130.2 (aromatic quaternary), 134.3 (aromatic quaternary), 139.5 ($\underline{C}H$=CH_2), 171 (C=N), 173 (C=O).

***N*-(diphenyl methylene)-allylgly-ala-OEt 238**



Palladium dibenzylidone acetone (23 mg, 0.025 mmol, 0.05 equivalents of Pd atoms) and DPPE (47 mg, 0.12 mmol, 0.24 equivalents of P atoms) were stirred together in THF (3 ml) for 10 min. Allyl acetate (0.15 ml, 1.39 mmol, 1.39 equivalents) was added and stirred for 10 min. *N*-(diphenyl methylene)-gly-ala-OEt (341 mg, 1.0 mmol, 1 equivalents) and BTTP (0.62 ml, 3.72 mmol, 1.25 equivalents), were stirred together in THF (2 ml) for 10 min. The Pd complex was added and stirred for 24 h. The solvent was removed and it was purified using "flash" column chromatography using EtOAc: Petrol 2:8 as eluent to give the *title compound* **238** as a colourless oil (156 mg, 0.41 mmol, 41 %). (Found: M^+ 379.2021, $C_{23}H_{26}N_2O_3$ requires M^+378.1943). ν_{max}/cm^{-1} (neat) 1739 (C=O), 1660 (C=C), 1598 (C=N) and 1511 (N-H). δ_H (270 MHz ; $CDCl_3$), 1.22 (3H, t, ***J*** 7.1, CH_3), 1.42 (3H, d, ***J*** 7.1, CH_3), 2.53 (2H, m, $C\underline{H}_2CH{=}CH_2$), 4.0 (1H, s, $C\underline{H}CONH$), 4.2 (2H, m, $C\underline{H}_2CH_3$), 4.6 (1H, m, ***J*** 7.1, $CHCO_2$), 5.0 (2H, m, $C\underline{H}_2{=}CH$), 5.71 (1H, m, $C\underline{H}{=}CH_2$), 7.1-7.8 (10H, m, $PhC\underline{H}$). δ_C (67.5 MHz ; $CDCl_3$) 14.1 (CH_3), 18.4 (CH_3), 39.7 ($\underline{C}H_2CH{=}CH_2$), 47.7 ($\underline{C}HCH_3$), 61.3 ($CO_2\underline{C}H_2$), 65.4 ($\underline{C}HCONH$), 117.6 ($\underline{C}H_2{=}CH$), 127.8 (Ph$\underline{C}$H), 128.1 (Ph$\underline{C}$H), 128.3 (Ph$\underline{C}$H), 128.6 (Ph$\underline{C}$H), 130.0 (Ph$\underline{C}$H), 130.6 (Ph$\underline{C}$H), 132.4 (Ph$\underline{C}$H), 133.9 (Ph$\underline{C}$H), 134.1 (Ph$\underline{C}$H), 135.8 (aromatic quaternary), 138 ($CH{=}CH_2$), 139.2 (aromatic quaternary), 169 (C=N), 172 (C=O), 174 (C=O).

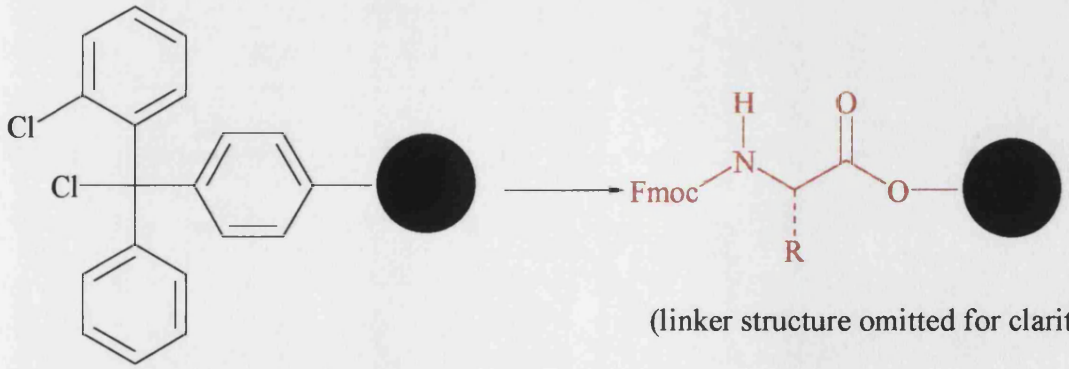
***N*-(diphenyl methylene)-allylgly-gly-OEt 120**



As above using petrol: EtOAc 25: 65 column eluent. To give the *title compound* **120** as a colourless oil (138 mg, 0.37 mmol, 37 %). ν_{max}/cm^{-1} (neat) 1738 (C=O), 1681 (C=C), 1601 (C=N) and 1535 (N-H). δ_H (270 MHz ; $CDCl_3$), 1.24 (3H, t, ***J*** 7.1, CH_3), 2.56 (2H, m, $CH_2CH=CH_2$), 4.07 (3H, m, CHCONH & CH_2CO_2), 4.22 (2H, m, CH_2CH_3), 5.07 (2H, m, CH_2=CH), 5.65 (1H, m, CH=CH_2) 7.1-7.8 (10H, m, PhCH). δ_C (67.5 MHz ; $CDCl_3$) 14.1 (CH_3), 39.7 ($CH_2CH=CH_2$), 40.9 (CH_2CH_3), 61.3 (CHCONH), 65.5 (CH_2CO_2), 117.6 (CH_2=CH), 127.8 (PhCH), 128.1 (PhCH), 128.6 (PhCH), 128.8 (PhCH), 130.6 (PhCH), 134.0 (PhCH), 135.7 (aromatic quaternary) 139.2 (aromatic quaternary), 169 (C=N), 172 (C=O), 174 (C=O).

(v) Loading of resins

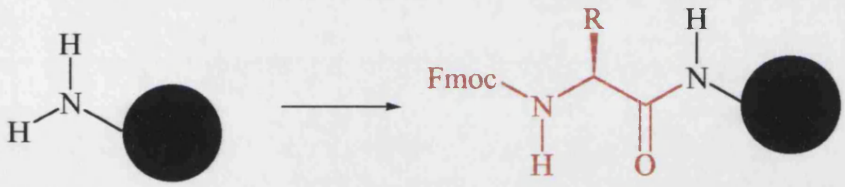
Representative procedure for the loading 2-chloro trityl chloride resin with Fmoc amino acids.



(linker structure omitted for clarity)

The 2-chloro trityl chloride resin (4g, 1.35 mmol/g loading of resin 5.4 mmol), was swollen in CH_2Cl_2 (30 ml). The Fmoc-amino acid (6.24 mmol, 1.15 equivalents) was dissolved in CH_2Cl_2 (70 ml) with Diisopropylethylamine (1.25 ml, 7.17 mmol, 1.32 equivalents). The resulting solution was added to the resin and stirred for 90 min.. The resin was washed successively with CH_2Cl_2:MeOH:DIPEA (9:1:1), MeOH, DMF, MeOH, CH_2Cl_2 and dried overnight in a vacuum oven. The loading of resin was calculated by accurately weighing a small portion of the resin (between 8-12 mg to three decimal places), and stirring it with 20 % piperidine in DMF (spectroscopic grade) for 1 hour. It was diluted with MeOH to 10 ml and the concentration of Fmoc-piperidine adduct calculated by measuring the absorption at 301 nm (ε = 7800), typical loading 31-40 % of theoretical yield.

Representative procedure for loading the TGR resin



(linker structure omitted for clarity)

The TGR resin was swollen in CH_2Cl_2 (6ml/g resin) and Fmoc amino acid (3 equivalents), HOBt (3 equivalents), DIPCDI (3 equivalents) sequentially added and shaken for 3 h. It was washed successively with MeOH followed by CH_2Cl_2 and this washing was repeated four times. The coupling was repeated and the Kaiser test was performed on a few milligrams of resin to see if any free NH_2 groups were still present. The reaction was repeated as necessary until a negative result was obtained. The resin was used in further reactions without drying.

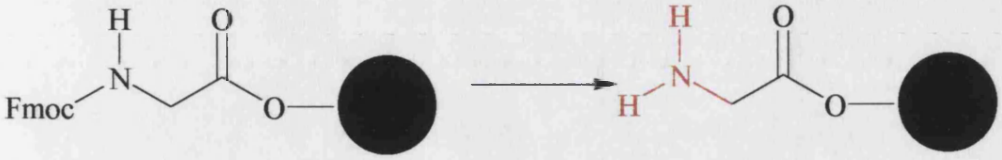
The procedure for the Kaiser test

The resin was heated for 5 min. at 100°C with 1 drop of each of the following phenol (42.5 mol dm^{-3} ethanolic solution), potassium cyanide (2 x 10^{-5} mol dm^{-3} in 49:1 pyridine:H_2O),

ninhydrin (0.56 mol dm^{-3} in EtOH). A blue colour absorbed on the beads indicated a positive result and no colouration on the beads indicated that NH_2 groups were absent.

(vi) Deprotection of amino acid/peptide attached to resin

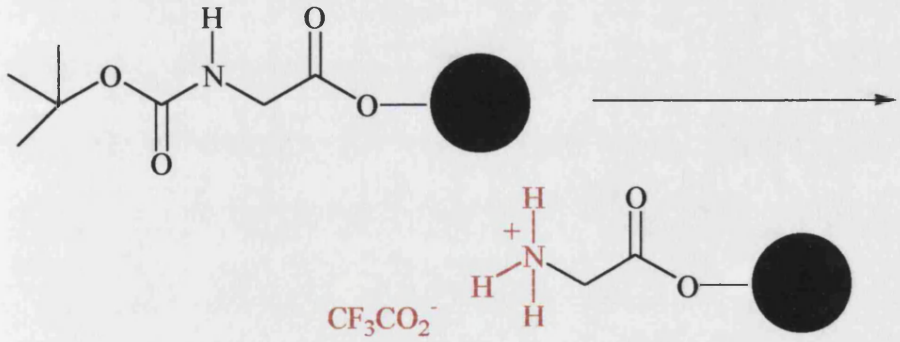
Representative procedure for deprotecting resin amino acid/ peptide Fmoc.



(linker structure omitted for clarity)

The resin was swollen in CH_2Cl_2 (6ml/ g resin) and piperidine (2ml/g resin) added and shaken for 1 hour. It was washed successively with MeOH / CH_2Cl_2 and this washing was repeated four times, the resin was used in further reactions without drying.

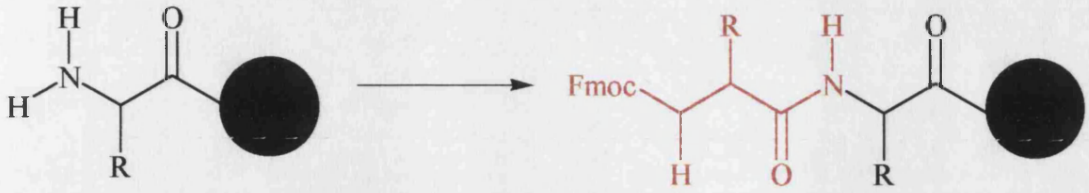
Representative procedure for deprotecting the Merrifield resin



The merrifield resin (5g, 3.5 mmol/g loading of resin 5.4 mmol), was swollen in CH_2Cl_2 (30 ml), CF_3CO_2H (10 ml, 129 mmol) was added and the reaction shaken for 2 hours. The resin was washed successively with CH_2Cl_2:MeOH:DIPEA (9:1:1), MeOH, DMF, MeOH, CH_2Cl_2 and dried overnight in a vacuum oven.

(vii) Extending the peptide chain

Representative procedure for extending the peptide chain

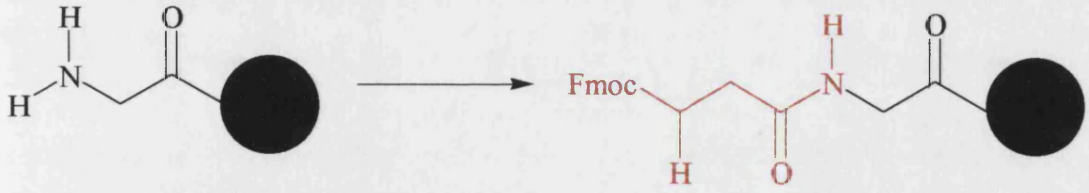


(this applies to either resin and any peptide chain)

The resin was swollen in CH_2Cl_2 (6ml/g resin) and Fmoc amino acid (3 equivalents), HOBt (3 equivalents), DIPCDI (3 equivalents) sequentially added and shaken for 2-3 h. It was washed successively with MeOH/CH_2Cl_2 and this washing was repeated four times. The coupling was repeated and the Kaiser test was performed on a few milligrams of resin to see if any free NH_2 groups were still present. The reaction was repeated as necessary until a negative result was obtained. The resin was used in further reactions without drying.

(viii) Formation of imines (solid phase)

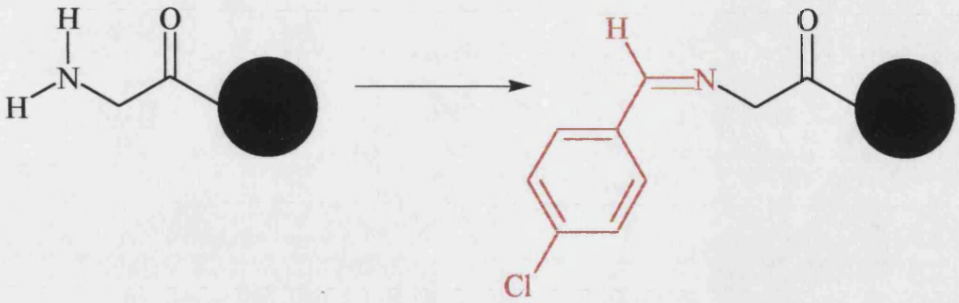
Representative procedure for forming the benzophenone derived imine



(linker structure not shown for clarity)

The deprotected resin was swollen in CH_2Cl_2 (6ml/ g resin) and benzophenone imine (10 equivalents), AcOH (0.1 equivalents) sequentially added and shaken for 24 h. It was washed successively with MeOH/CH_2Cl_2 and this washing was repeated four times. The coupling was repeated and the Kaiser test was performed on a few milligrams of resin to see if any free NH_2 groups were still present. The reaction was repeated as necessary until a negative result was obtained. The resin was dried in a vacuum oven.

Representative procedure for forming the *p*-chlorobenzaldehyde derived imine

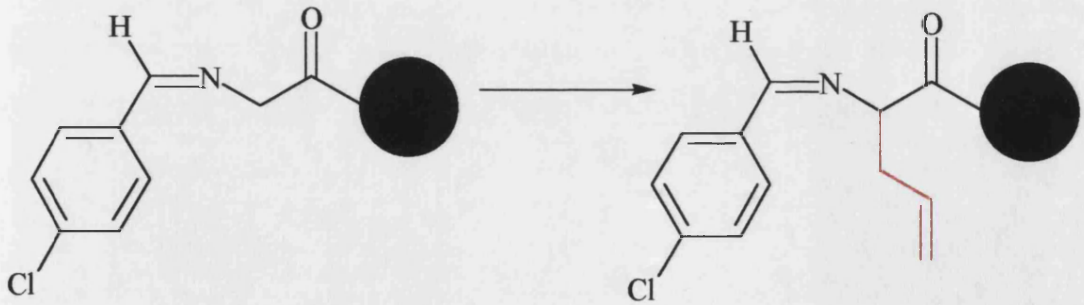


(linker structure and peptide chain not shown for clarity)

The deprotected resin was swollen in CH_2Cl_2 (6ml/g resin) and *p*-chlorobenzaldehyde (3.5 equivalents), trimethyl orthoformate (5.5 equivalents) sequentially added and shaken for 24 h. It was washed successively with MeOH/CH_2Cl_2 and this washing was repeated four times. The coupling was repeated and the Kaiser test was performed on a few milligrams of resin to see if any free NH_2 groups were still present. The reaction was repeated as necessary until a negative result was obtained. The resin was dried in a vacuum oven.

(ix) Palladium catalysed allylation (solid phase)

Representative procedure for Palladium catalysed allylation of the activated amino acid or peptide



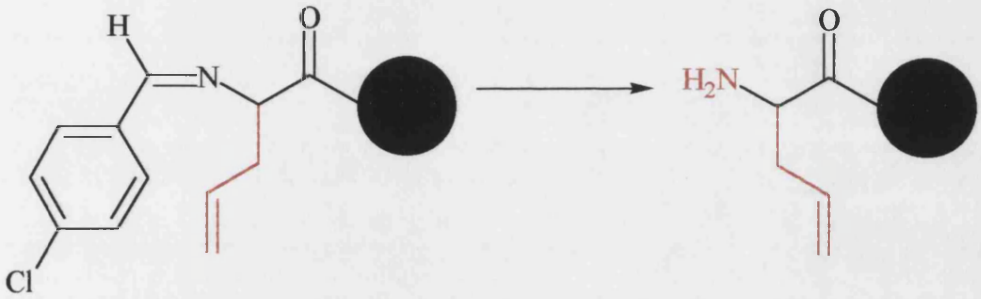
(linker structure and peptide chain not shown for clarity)

The resin was swollen in DMF (or CH_2Cl_2 or THF(4ml/ g resin) and shaken for 15 min. Phosphazene base (2 equivalents) was added and shaken for fifteen min. The Pd complex was

formed by stirring $Pd_2(dba)_3$ ligand (ratio of donor atom : palladium 2:1) in the minimum amount of DMF or THF for 10 min, electrophile (25 equivalents) was added and stirred for 15 min. The preformed Pd complex was added to the resin and shaken for 72 h. It was washed successively with $MeOH/CH_2Cl_2$ and this washing was repeated four times. The reaction was then repeated for 24 h. and the resin was washed successively with $MeOH/CH_2Cl_2$ and this washing was repeated four times. The resin was used in further reactions without drying.

(x) Removal of imine (solid phase)

Representative procedure for removing the imine

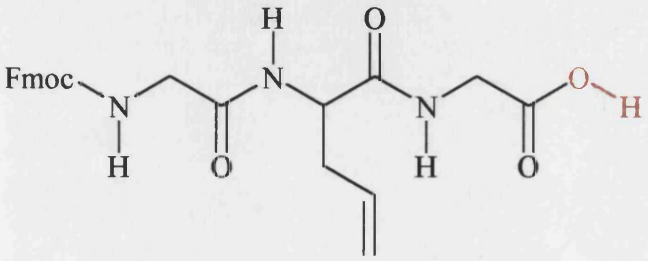


(linker structure and peptide chain not shown for clarity)

The resin was shaken with a 1:1 mixture of CH_2Cl_2 : NH_2OH (50 % w/w aqueous) (8ml/ g resin) for 24 h. It was washed successively with $MeOH/CH_2Cl_2$ - this washing was repeated four times. The reaction was repeated three times to ensure complete removal of the imine. The resin was used in further reactions without drying.

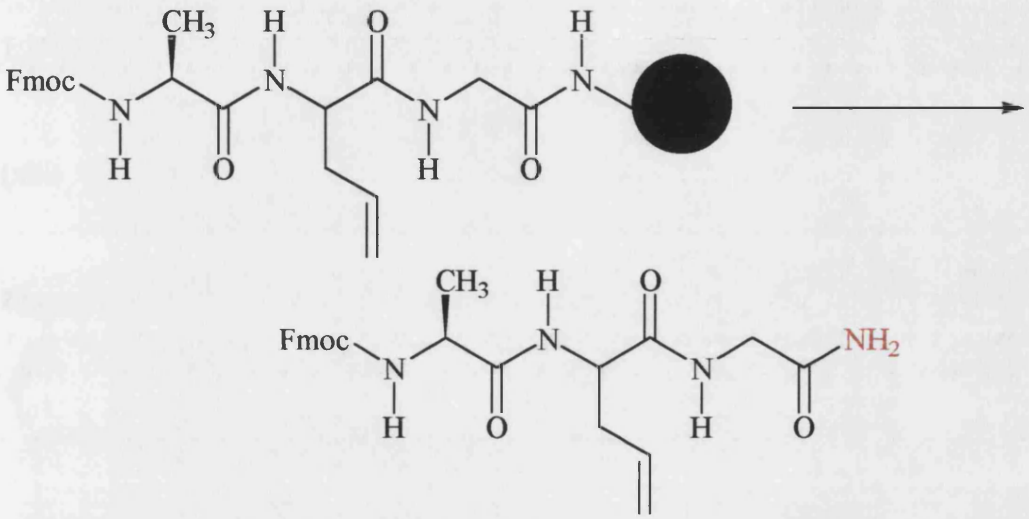
(xi) Cleavage of peptide from resin

Representative procedure for cleavage of peptide from 2 chlorotrityl chloride resin



The resin (0.4 g) was shaken with CH_2Cl_2 (2 ml) for five min. and a mixture of CH_2Cl_2 (2.5 ml), H_2O (0.25 ml), CF_3CO_2H (0.25 ml) added, they were then shaken for 4 h. and washed with MeOH, CH_2Cl_2, H_2O. The liquors were combined and evaporated to dryness. The crude material was purified by HPLC.

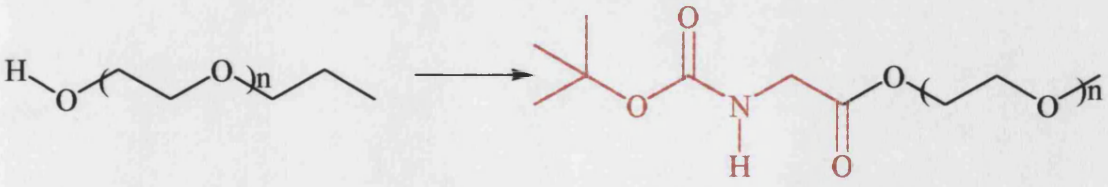
Representative procedure for cleavage of peptide from Tentagel amide resin



The resin (0.5 g) was shaken with a mixture of $(CH_3)_2S$ (0.2 ml), H_2O (0.22 ml) and CF_3CO_2H (3.6 ml) for 16 h., then washed with MeOH, CH_2Cl_2, H_2O. The liquors were then combined and evaporated to dryness. The crude material was purified by HPLC.

(xii) Liquid phase chemistry

^{t}Boc-gly-methoxy polyethylene glycol 191

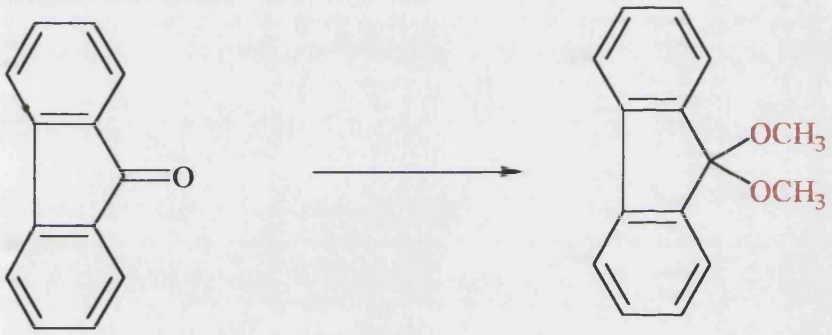


^{t}Boc-gly-(0.209 g, 1.2 mmol, 1.2 equivalent), methoxy polyethylene glycol (3.33g, 1 mmol, 1 equivalent), 1,3 dicyclohexylcarbodiimide (0.246 g, 1.19 mmol, 1.2 equivalent) and dimethyl

amino pyridine (0.146 g, 1.2 mmol, 1 equivalent) were stirred together in CH_2Cl_2 (200 ml) for 16 h. The dicyclohexylurea was filtered out of the solution and Et_2O (150 ml) was added. After cooling at 0°C for 1 hour the polymer was precipitated and removed by filtration to give the *title compound* **191** as a colourless solid (3.33 g, 0.95 mmol, 95 %). As this was just the first step in the (ultimately unsuccessful) route, the compound was not fully characterised and was taken through to the next step as a crude mixture. ^1H NMR spectrum indicated the presence of the ^{t}Boc group and the CH_3 signal could be seen in the ^1H NMR spectrum at 1.39 ppm.

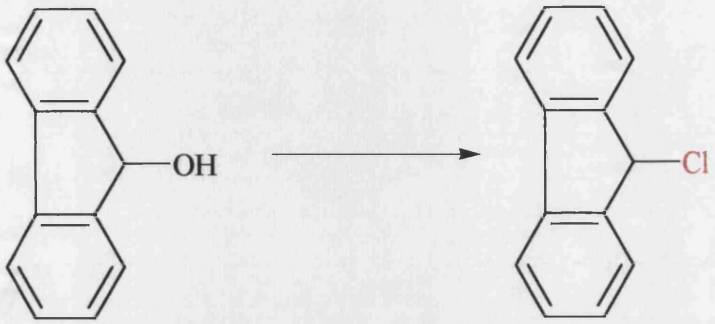
(xiii) Synthesis of 9-fluorenone imine and imines derived from it

Fluorenone acetal 212



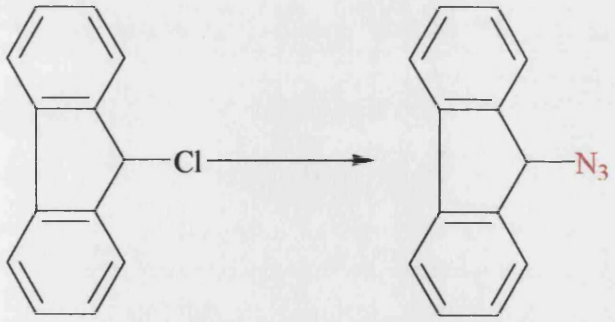
Flourenone (13.16 g, 73 mmol, 1 equivalent), tosyl acid (0.55g, 3.26 mmol, 4.5 % equivalent), and trimethyl orthoformate (17.5ml, 160 mmol, 2.1 equivalents), were stirred in MeOH for 40 h. and ammonia in MeOH (10ml, 20 mmol) was then added. The solvent was removed *in vacuo* and the crude product dissolved in CH_2Cl_2. This was filtered to remove the ammonium tosylate and the solvent removed *in vacuo* to give the *title compound* **212** as a yellow solid (14.1 g, 62 mmol, 86 %). δ_H (270 MHz ; $CDCl_3$) 3.3 (6H, s, OCH_3), 7.2-7.6 (8H, m, ArC<u>H</u>). δ_C (75 MHz ; $CDCl_3$) 51.3 (OCH_3), 108.5 (<u>C</u>$(OCH_3)_2$), 120.2 (Ar<u>C</u>H), 124.7 (Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 138 (C-quaternary aromatic), 142 (C-quaternary aromatic).

Preparation of 9 chlorofluorene 215



9 Hydroxy fluorene (4.95 g, 27.2 mmol, 1 equivalent) was dissolved in hydrochloric acid (100 ml, 36 %, 980 mmol) and heated at reflux for 20 h. The solution was washed (CH_2Cl_2 100 ml x 3). The combined organic layers were dried ($MgSO_4$), and the solvent removed *in vacuo* to give the *title compound* **215** as a colourless solid (3.74 g, 18.6 mmol, 68 %). δ_H (270 MHz ; $CDCl_3$), 5.8 (1H, s, CHCl), 7.2-7.8 (8H, m, ArCH). δ_C (75 MHz ; $CDCl_3$) 51.5 (CHCl), 120.4 (ArCH), 126.3 (ArCH), 130.4 (ArCH), 132.2 (ArCH), 138 (C-quaternary aromatic), 142 (C-quaternary aromatic).

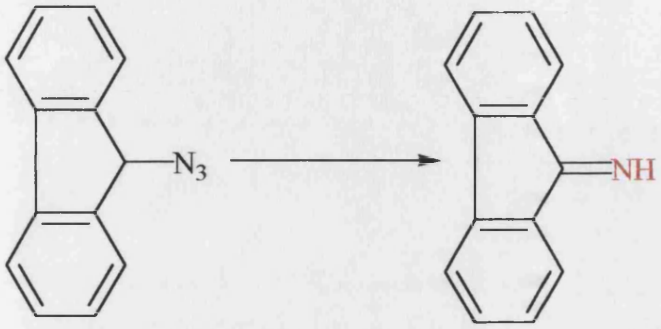
9 Fluorene azide 216



9 chlorofluorene (4.95 g, 27.2 mmol, 1 equivalent) and NaN_3 (it is important to be careful with NaN_3 as it is explosive and toxic) (16.87g, 260 mmol, 3 equivalents) were dissolved in MeOH (200 ml) and heated at reflux for 4 h. The solution was mixed with H_2O (400ml) and the organic material extracted (petrol : EtOAc 1:1 200 ml x 4). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to give a brown liquid which crystallised to give the *title compound* **216** as a brown solid (16.3 g, 78.6 mmol, 93 %). δ_H

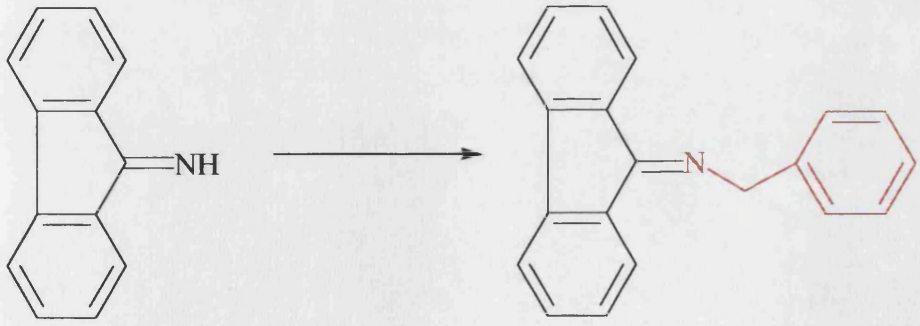
(270 MHz ; $CDCl_3$), 5.2 (1H, s, CHN_3), 7.2-7.8 (8H, m, ArCH). δ_C (75 MHz ; $CDCl_3$) 63.5 (CHN_3), 119.9 (ArCH), 122.1 (ArCH), 122.1 (ArCH), 126.0 (ArCH), 128.0 (ArCH), 130 (C-quaternary aromatic), 142 (C- quaternary aromatic).

9-fluorenone imine 207



9 Flourene azide (20.00 g, 97 mmol) was carefully heated at 90°C for 2 h (great care should be taken while doing this). The liquid was poured into Et_2O and the solid material filtered off to give the *title compound* **207** as a brown solid (8.3 g, 46.4 mmol, 48%). ν_{max}/cm^{-1} IR 3000 (C-H) 1449 (N=N). δ_H (270 MHz ; $CDCl_3$) 7.2-7.6 (8H, m, ArCH), 7.8 (1H, s, NH) . δ_C (75 MHz ; $CDCl_3$) 119.9 (ArCH), 122.1 (ArCH), 128.0 (ArCH), 128.0 (ArCH), 142 (C-quaternary aromatic), 172 (C=NH).

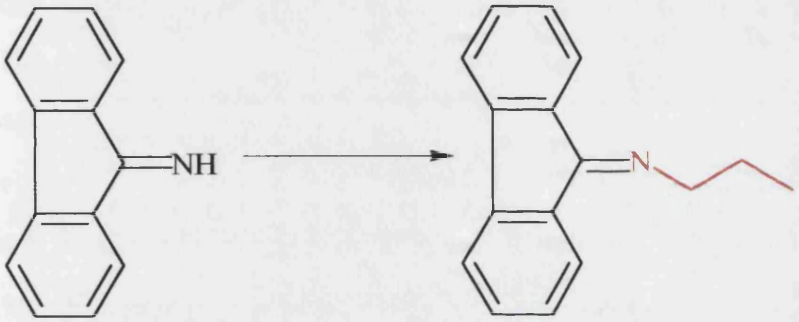
***N*-(9H Fluorene-9-ylidine) benzyl 208**



9 Flourene imine (1.1 g, 6 mmol, 1 equivalent) and benzyl amine (0.72 ml, 6.6 mmol, 1.1 equivalents) were dissolved in CH_2Cl_2 (80 ml) and stirred for 24 h. The solution was removed *in vacuo* to give to the *title compound* **208** as a red oil. It was dissolved in petrol :

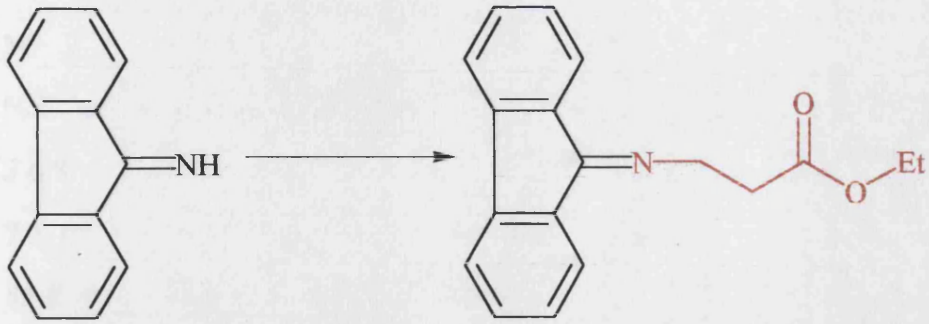
EtOAc (9:1) and filtered through a short plug of silica to give an orange solid (970 mg, 3.63 mmol, 60%). ν_{max}/cm^{-1} 3000 (C-H) 1449 (C=N). δ_H (270 MHz ; $CDCl_3$) 5.4 (2H, s, CH_2Ph), 7.2-7.6 (8H, m, ArCH). δ_C (75 MHz ; $CDCl_3$) 56.7 (CH_2), 120.3 (ArCH), 121.5 (ArCH), 122.8 (ArCH), 125.9 (ArCH), 126.3 (ArCH), 127.8 (ArCH), 128.7 (ArCH), 129.5 (ArCH), 131.4 (ArCH), 132.3 (ArCH), 136 (C-quaternary aromatic), 138 (ArCH), 140 (C-quaternary aromatic), 142 (C-quaternary aromatic), 168 (C=NH).

_N_-(9H Fluorene-9-ylidine) propane 217



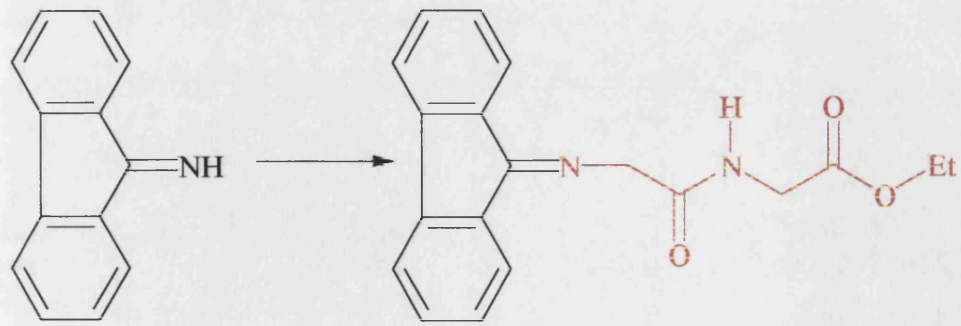
9 Fluorene imine (236mg, 1.32 mmol, 1 equivalent) and propyl amine (0.12 ml, 1.45 mmol, 1.1 equivalents) were dissolved in CH_2Cl_2 (30 ml) and stirred for 48 h. The solvent and excess propyl amine were removed *in vacuo* to give the *title compound* **217** as an orange oil (246 mg, 1.1 mmol, 84%). δ_H (270 MHz ; $CDCl_3$), 1.11 (3H, t, ***J***, 7.4, CH_2CH_3), 1.96 (2H, q, ***J*** 7.4, 7.2 CH_2CH_3), 4.09 (2H, t, ***J*** 7.2, CH_2CH_2Me), 7.2-7.9 (8H, m, ArCH). δ_C (75 MHz ; $CDCl_3$) 12.2 (CH_3), 24.8 (CH_2), 55.7 (CH_2N), 119.3 (ArCH), 120.2 (ArCH), 127.6 (ArCH), 126 (ArCH), 127.9 (ArCH), 130.6 (ArCH), 131.0 (ArCH), 132.0 (ArCH), 138.5 (ArCH), 140 (C-quaternary aromatic), 143 (C-quaternary aromatic), 162 (C=N).

***N*-(9H Fluorene-9-ylidine)-β ala-OEt 218**



9 Flourene imine (1.175g, 6.23 mmol, 1 equivalents) and β alanine ethyl ester hydrochloride (1.2 g, 7.29 mmol, 1.1 equivalents) were dissolved in CH_2Cl_2 (100 ml) and stirred for 48 h. The mixture was washed (H_2O (50 ml x 2)) and the solvent was removed *in vacuo* to give the *title compound* **218** as a yellow solid (1.29 g, 4.62 mmol, 74%). M. p. 132-133 °C. ν_{max}/cm^{-1} 1719 (C=O), 1611 (C=N), 1449 (C=C). δ_H (270 MHz; $CDCl_3$), 1.25 (3H, t, ***J*** 6.8, $CH_2\underline{CH_3}$), 2.96 (2H, t, ***J*** 7.3, $\underline{CH_2}CO_2H$), 4.18 (2H, q, ***J*** 6.8, $\underline{CH_2}CH_3$), 4.36 (2H, t, ***J*** 7.3, $\underline{CH_2}CH_2$), 7.2-7.9 (8H, m, Ar$\underline{CH}$), 8.1 (1H, s, NH) . δ_C (75 MHz ; $CDCl_3$) 14.2 (CH_3), 36.6 ($\underline{CH_2}CO_2$), 48.9 ($\underline{CH_2}CH_3$), 60.3 ($\underline{CH_2}CH_2$), 119.2 (Ar$\underline{CH}$), 120.2 (Ar$\underline{CH}$), 122.3 (Ar$\underline{CH}$), 127.5 (Ar$\underline{CH}$), 127.9 (Ar$\underline{CH}$), 128,1 (Ar$\underline{CH}$), 130.7 (Ar$\underline{CH}$), 138 (C-quaternary aromatic), 140 (C-quaternary aromatic), 143 (C-quaternary aromatic), 162 (C=N), 173 (C=O).

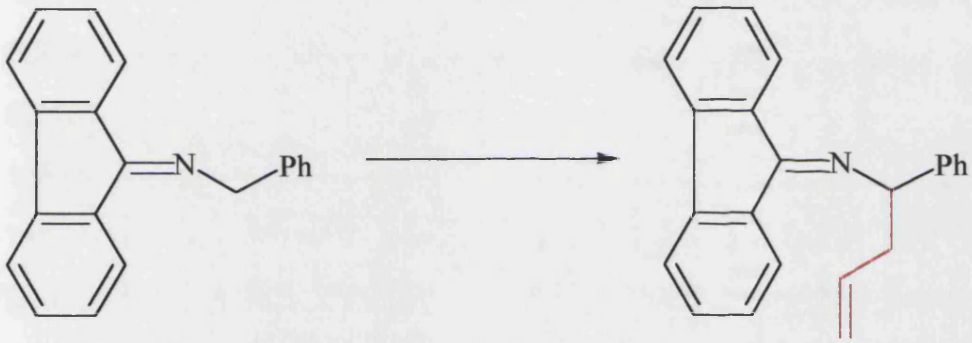
***N*-(9H Fluorene-9-ylidine)-gly-gly-OEt 219**



9 Flourene imine (1.2g, 6.7 mmol, 1 equivalent) and gly-gly-ethyl ester hydrogen chloride (1.5 g, 7.63 mmol, 1.14 equivalent) were dissolved in CH_2Cl_2 (110 ml) and stirred for 48 h. The

reaction mixture was washed (H_2O (50 ml x 2)), dried ($MgSO_4$) and the solvent was removed *in vacuo* to give the *title compound* **219** as a yellow solid (1.43 g, 4.43 mmol, 66%). (Found: M^+ 322.1313, $C_{19}H_{18}N_2O_3$ requires M^+ 322.1317), (Found: C 70.3 %, H 5.58 %, N 8.53 % $C_{18}H_{22}N_2O_3$ requires 70.8 %, 5.60 % and 8.70 %). δ_H (270 MHz ; $CDCl_3$), 1.25 (3H, t, *J* 6.8, $CH_2\underline{CH_3}$), 2.96 (2H, t, *J* 7.3, $\underline{CH_2}CO_2H$), 4.18 (2H, q, *J* 6.8, $\underline{CH_2}Me$), 4.36 (2H, t, *J* 7.3, $\underline{CH_2}CH_2$), 7.2-7.9 (8H, m, Ar$\underline{CH}$) . δ_C (75 MHz ; $CDCl_3$) 14.1 ($\underline{CH_3}$), 41.2 ($\underline{CH_2}CH_3$), 55.2 ($\underline{CH_2}CO_2$), 61.5 (CH_2CONH), 119 (Ar$\underline{CH}$), 120.2 (Ar$\underline{CH}$), 120.5 (Ar$\underline{CH}$), 124.2 (Ar$\underline{CH}$), 127.5 (Ar$\underline{CH}$), 128.4 (Ar$\underline{CH}$), 131.5 (Ar$\underline{CH}$), 131.7 (Ar$\underline{CH}$), 137.5 (C-H aromatic), 141.2 (C-quaternary aromatic), 143.8 (C-quaternary aromatic), 163.7 (C=N), 169.8 (C=O), 170.7 (C=O).

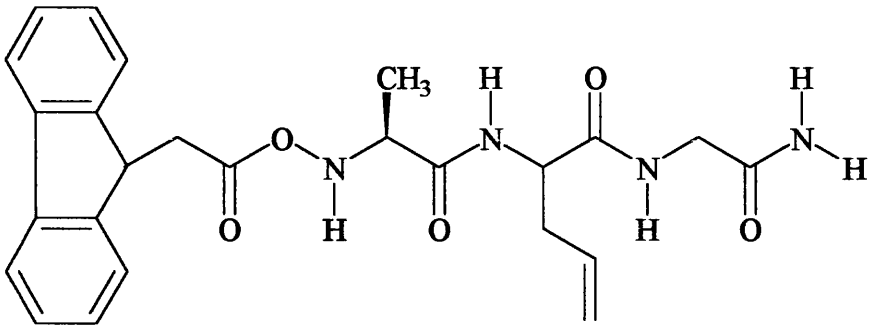
(xiv) General procedure for attempted allylation of Fluorene imines



Palladium dibenzylidone acetone (23 mg, 0.025 mmol, 0.05 equivalents of Pd atoms) and DPPE (47 mg, 0.12 mmol, 0.24 equivalents of P atoms) were stirred together in THE or DMF (3 ml) for 10 min. Allyl acetate (0.15 ml, 1.39 mmol, 1.39 equivalents) was added and stirred for 10 min. Imine (1.0 mmol, 1 equivalents) and Base (phosphazene base or NaH or LDA or LDA/^{t}KBuO , 1.25 equivalents), were stirred together in THF (2 ml) for at least 10 min. The Pd complex was added and stirred for at least 24 h. The reaction was followed by tlc, heating the reaction at reflux was tried.

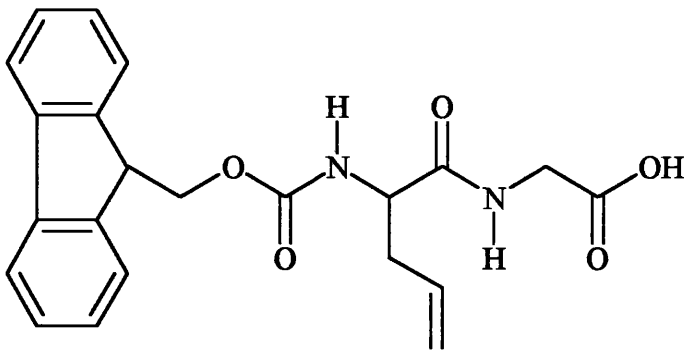
(xv) Analytical information for allylated dipeptides

Fmoc-ala-allylgly-gly-NH_2 222



The *title compound* **222** was a deliquescent solid/oil. δ_H (400 MHz ; $(CD_3)_2SO$), 1.3 (3H, m, CH_3), 2.3-2.4 (2H, m, $CH_2CH{=}CH$), 3.5 (2H, CH_2CHFluorenyl), 4.1 (1H, m, $CHCH_3$), 4.3 (4H, m, $CHCH_2CH$, CH_2CONH_2 and CH-Fluorenyl), 5.0 (2H, m, $CH_2{=}CH$), 5.5 (1H, m, $CH{=}CH_2$), 7.1-7.8 (10H, m, PhCH). δ_C (100 MHz ; $(CD_3)_2SO$) 18.1 (CH_3), 36.2 ($CH_2CH{=}CH$), 46.1 (CHFluorenyl), 50.1 ($CHCH_3$), 51.5 ($CHCH_2CH{=}CH$), 65.6 (CH_2CONH_2), 69.7 (CH_2CHFluorenyl), 117.3 ($CH{=}CH_2$), 120.1 (C-H aromatic), 125.3(C-H aromatic), 127.0 (C-H aromatic), 127.6 (C-H aromatic), 134.0(C-H aromatic), 134.2 (C-H aromatic), 140.7 ($CH_2{=}CH$), 143.7 (aromatic quaternary), 143.8 (aromatic quaternary), 155.8 (CO_2), 172.1 (CO), 172.3 (CO), 172.6 (CO), 172.7 (CO).

Fmoc-gly-allygly-gly-OH 185

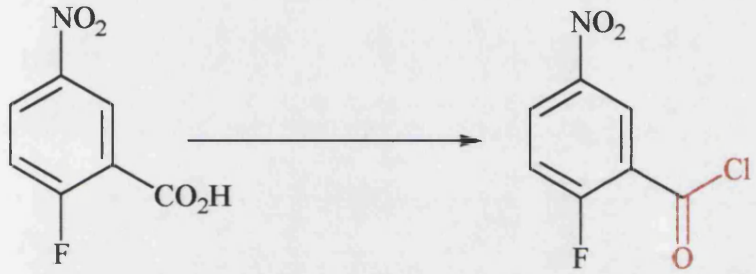


The *title compound* **185** was a deliquescent solid/oil. δ_H (400 MHz ; $(CD_3)_2SO$), 2.3-2.4 (2H, m, $CH_2CH{=}CH$), 3.5 (2H, CH_2CHFluorenyl), 4.1 (2H, m, CH_2 gly), 4.3 (4H, m,

CHCH$_2$CH, CH$_2$CONH$_2$ and CH-Fluorenyl), 5.0 (2H, m, CH$_2$=CH), 5.7 (CH=CH$_2$) -7.8 (10H, m, PhCH). δ_C (100 MHz ; (CD$_3$)$_2$SO) 36.5 (CH$_2$CH=CH), 46.6 (CH$_2$CO$_2$H), 46.1 (CH$_2$CHFluorenyl), 51.8 (CH-allyl), 65.6 (CH$_2$CONH), 69.7 (CH$_2$ of Fmoc), 117.5 (CH=CH$_2$), 120.1 (PhCH), 125.2 (PhCH), 126.4 (PhCH), 127.0 (PhCH), 127.6 (PhCH), 128.5 (PhCH), 129.1 (PhCH), 129.6 (PhCH), 132.7 (PhCH), 134.0 (PhCH), 140.7 (CH$_2$=CH), 143.8 (aromatic quaternary), 143.8 (aromatic quaternary), 156.4 (CO$_2$), 168.8 (CO), 170.9 (CO), 171.2 (CO).

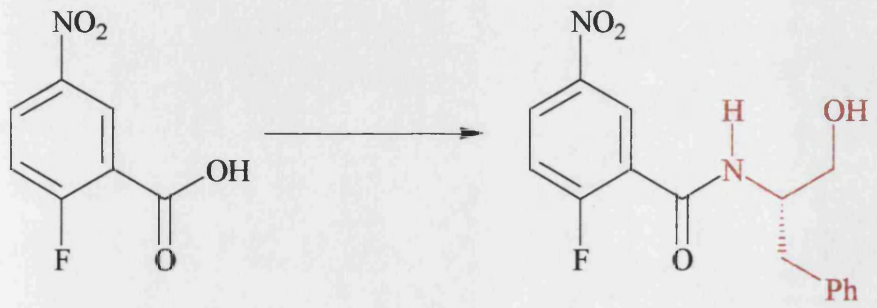
(xvi) Attempted synthesis of oxazoline ligands attached to resin.

Preparation of 2 Fluoro-5-nitrobenzyl chloride 248



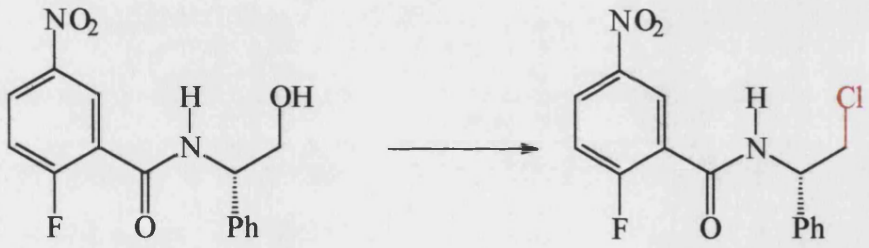
2-fluoro 5 nitrobenzoic acid (970 mg, 5.87 mmol, 1 equ.), SOCl$_2$ (0.4ml, 5.5 mmol, 5 equ.), CH$_2$Cl$_2$ (50 ml) and HCON(CH$_3$)$_2$ catalytic were refluxed together for 90 min. and the reaction mixture was then left stirring for 50 h. at room temperature. The solvent was removed to give the *title compound* **248** as a white solid (970 mg, 4.76 mmol, 81%). The IR showed the C=O bond change from 1700 to 1760 cm^{-1}. It was then used without further analysis.

Preparation of 2 Fluoro-5-nitrobenzyl chloride alaninol 249



L-phenyl alaninol (752 mg, 5 mmol, 1 equ.), 2-fluoro 5 nitrobenzoic acid (980 mg, 6.75 mmol, 1.36 equ.), HOAt (699 mg, 5.1 mmol, 1 equ.) and 1-ethyl-3(3'-dimethylaminopropyl) carbodiimide HCl (1.033g, 5.4 mmol, 1.1 equ.) were stirred together in a mixture of CH_2Cl_2 (50 ml) and EtOAc (30 ml). The reaction was followed by tlc and after 20 h. had gone to completion. The reaction mixture was washed ($NaOH_{(aq)}$ (1 mol dm^3) 50 ml x 1), ($HCl_{(aq)}$ (1 mol dm^3) 50ml x 1), (H_2O (50 ml x 1), dried ($MgSO_4$) and filtered through a short plug of silica. The solvent was then removed *in vacuo* to give the *title compound* **249** as a white powder (1.56 g, 4.73 mmol, 95 %). δ_H (275 MHz ; $CDCl_3$), 2.1- 2.5 (1H, bs, OH) 3.05 (2H, d, ***J*** 7.2 $C\underline{H}_2OH$), 3.75 (2H, m, $C\underline{H}_2Ph$), 4.51 (1H, m, $C\underline{H}CH_2Ph$) 6.98 (1H, bs NH), 7.1 (5H, m, aromatic CH), 8,4 (1H, m, aromatic CH), 9.0 (2H, m, aromatic CH). δ_C (75 MHz) 37.4 ($\underline{C}H_2Ph$), 53.9 ($\underline{C}HCH_2Ph$), 64.0 ($\underline{C}H_2OH$), 127.3 (C aromatic), 128.7 (C-H aromatic), 128.9 (C-H aromatic), 129.2 (C-H aromatic), 129.3 (C-H aromatic), 129.3 (C-H aromatic), 164 (C=O).

Preparation of 2 Fluoro-5-nitrobenzyl chloride alaninol chloride 250



Benzamide (242) (1.44 g, 4.52 mmol, 1 equ.) was dissolved in CH_2Cl_2 and $SOCl_2$ (2 ml, 27.2 mmol, 6 equ.) added slowly. The reaction was heated at reflux for 2 h. The solvent was removed under *in vacuo* to give the *title compound* **250** as a yellow solid (1.5 g, 4,46 mmol, 99 %).δ_H (275 MHz ; $CDCl_3$), 3.05 (2H, m, $C\underline{H}_2Cl$), 3.61 (1H, dd, ***J*** 8.2 and 3.1) $C\underline{H}Ph$), 3.75 (1H, dd, ***J*** 8.2 and 3.1) $C\underline{H}Ph$), 4.55 (1H, m, $C\underline{H}CH_2Ph$) 6.98 (1H, bs NH), 7.15 (5H, m, C_6H_5), 8.35 (1H, m, aromatic CH), 8.8 (2H, m, aromatic CH). δ_C (75 MHz) 37.9 ($\underline{C}H_2Ph$), 46.6 ($\underline{C}H_2Cl$), 50.7 ($\underline{C}HCH_2Ph$), 127.3 (C aromatic), 128.6 (C-H aromatic), 128.7 (C-H

aromatic), 129.1 (C-H aromatic), 129.3 (C-H aromatic), 130.3 (C-H aromatic), 136.7 (C-CO), 161.8 (C-F) 165.9 (C=O).

Chapter 6

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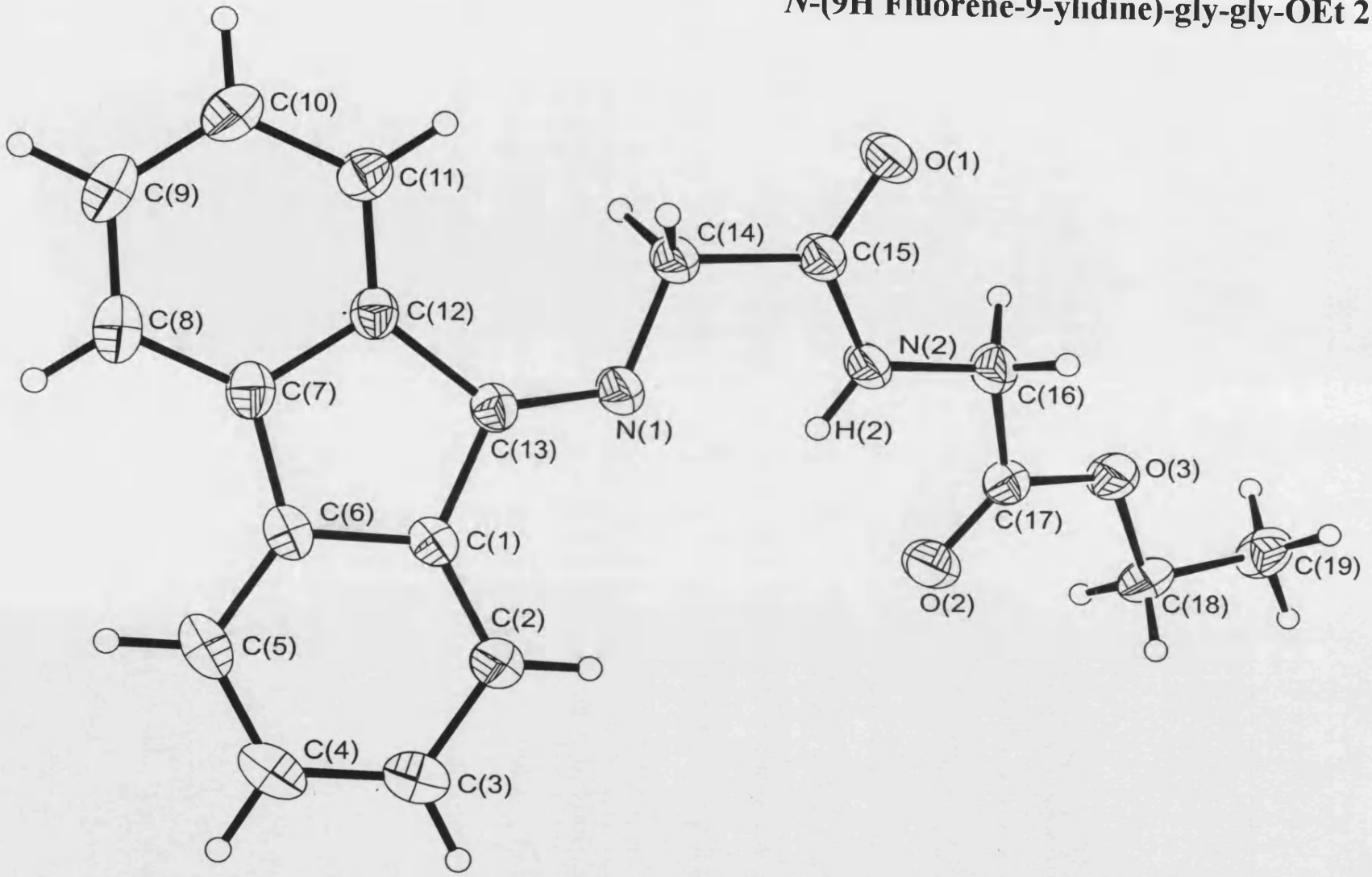
Chapter 7

X-ray structure Report

_N_-(9H Fluorene-9-ylidine)-gly-gly-OEt 219



NOTE ON 98JMJW4/D.HOLLAND(1)

A crystal of approximate dimensions 0.2 x 0.2 x 0.2 mm was used for data collection.

Crystal data: $C_{19}\ H_{18}\ N_2\ O_3$, M = 322.35, Monoclinic , a = 8.944(1), b = 9.579(1), c = 19.216(2) Å , β = 99.85(1)^o, U = 1622.1(3) Å^3, space group $P2_1/c$, Z = 4, D_c = 1.320 gcm^{-3}, μ(Mo-K_α) = 0.090 mm^{-1}, F(000) = 680. Crystallographic measurements were made at 293(2)^o K on a CAD4 automatic four-circle diffractometer in the range 2.15<θ<24.97^o. Data (3119 reflections) were corrected for Lorentz and polarization and also for extinction.

In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions where relevant.

The solution of the structure (SHELX86)[1] and refinement (SHELX93)[2] converged to a conventional [i.e. based on 2211 F^2 data with $Fo>4\sigma(Fo)$] $R1$ = 0.0398 and $wR2$ = 0.1141. Goodness of fit = 0.903. The max. and min. residual densities were 0.201 and -0.170 eÅ^{-3} respectively. The asymmetric unit (shown in Fig. ...), along with the labelling scheme used was produced using ORTEX.[3] Final fractional atomic co-ordinates and isotropic thermal parameters, bond distances and angles are given in Tables ... , ... and ... respectively. Tables of anisotropic temperature factors are available as supplementary data.

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2. Sheldrick G.M., SHELXL, a computer program for crystal structure refinement, University of Göttingen, 1993.

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Footnote:

Interesting intramolecular distances and angles in the region of H2 are as follows: [H2-N1 2.290(2), H2-O2 2.406(2)Å; N2-H2-N1 108.71(4), N2-H2-O2 102.82(4)^o]

Table 1. Crystal data and structure refinement for 1.

Identification code	98JMJW4/D.HOLLAND(1)
Empirical formula	$C_{19}H_{18}N_2O_3$
Formula weight	322.35
Temperature	293(2)°K
Wavelength	0.71069 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 8.944(1)Å
	b = 9.579(1)Å β = 99.85(1)°
	c = 19.216(2)Å
Volume	1622.1(3) $Å^3$
Z	4
Density (calculated)	1.320 Mg/m^3
Absorption coefficient	0.090 mm^{-1}
F(000)	680
Crystal size	0.2 x 0.2 x 0.2 mm
Theta range for data collection	2.15 to 24.97 °.
Index ranges	-10<=h<=0; 0<=k<=11; -22<=l<=22
Reflections collected	3119
Independent reflections	2857 [R(int) = 0.0402]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2852 / 0 / 220
Goodness-of-fit on F^2	0.903
Final R indices [I>2σ(I)]	R1 = 0.0398 wR2 = 0.1141
R indices (all data)	R1 = 0.0537 wR2 = 0.1227
Largest diff. peak and hole	0.201 and -0.170 $eÅ^{-3}$
Weighting scheme	calc $w=1/[\sigma^2(Fo^2)+(0.0949P)^2+0.1063P]$ where $P=(Fo^2+2Fc^2)/3$
Extinction coefficient	0.0092(23)
Extinction expression	$Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
N(1)	9269(1)	1859(1)	8675(1)	44(1)
N(2)	7437(1)	3343(1)	7686(1)	47(1)
O(1)	6156(1)	1437(1)	7239(1)	61(1)
O(2)	8315(1)	6066(1)	7648(1)	66(1)
O(3)	6434(1)	6518(1)	6747(1)	53(1)
C(1)	11284(2)	2002(2)	9678(1)	41(1)
C(2)	11242(2)	3380(2)	9885(1)	50(1)
C(3)	12270(2)	3824(2)	10466(1)	60(1)
C(4)	13331(2)	2917(2)	10825(1)	62(1)
C(5)	13387(2)	1536(2)	10612(1)	56(1)
C(6)	12358(2)	1080(2)	10039(1)	43(1)
C(7)	12115(2)	-302(2)	9707(1)	44(1)
C(8)	12899(2)	-1535(2)	9869(1)	58(1)
C(9)	12434(2)	-2714(2)	9471(1)	63(1)
C(10)	11211(2)	-2672(2)	8932(1)	58(1)
C(11)	10413(2)	-1439(2)	8764(1)	48(1)
C(12)	10872(2)	-243(2)	9149(1)	40(1)
C(13)	10308(1)	1237(2)	9099(1)	39(1)
C(14)	8315(2)	1070(2)	8126(1)	47(1)
C(15)	7193(2)	1965(2)	7649(1)	43(1)
C(16)	6536(2)	4282(2)	7201(1)	50(1)
C(17)	7221(2)	5710(2)	7238(1)	45(1)
C(18)	6826(2)	7992(2)	6764(1)	56(1)
C(19)	5737(2)	8687(2)	6193(1)	63(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

N(1)-C(13)	1.274(2)
N(1)-C(14)	1.450(2)
N(2)-C(15)	1.337(2)
N(2)-C(16)	1.439(2)
O(1)-C(15)	1.219(2)
O(2)-C(17)	1.196(2)
O(3)-C(17)	1.326(2)
O(3)-C(18)	1.453(2)
C(1)-C(2)	1.381(2)
C(1)-C(6)	1.398(2)
C(1)-C(13)	1.485(2)
C(2)-C(3)	1.385(2)
C(3)-C(4)	1.381(2)
C(4)-C(5)	1.388(3)
C(5)-C(6)	1.379(2)
C(6)-C(7)	1.470(2)
C(7)-C(8)	1.382(2)
C(7)-C(12)	1.407(2)
C(8)-C(9)	1.387(3)
C(9)-C(10)	1.371(3)
C(10)-C(11)	1.389(2)
C(11)-C(12)	1.388(2)
C(12)-C(13)	1.502(2)
C(14)-C(15)	1.506(2)
C(16)-C(17)	1.496(2)
C(18)-C(19)	1.493(2)
C(13)-N(1)-C(14)	119.67(13)
C(15)-N(2)-C(16)	120.92(12)
C(17)-O(3)-C(18)	117.01(13)
C(2)-C(1)-C(6)	120.73(13)
C(2)-C(1)-C(13)	130.23(13)
C(6)-C(1)-C(13)	109.04(13)
C(1)-C(2)-C(3)	118.6(2)
C(4)-C(3)-C(2)	120.9(2)
C(3)-C(4)-C(5)	120.6(2)
C(6)-C(5)-C(4)	118.9(2)

C(5)-C(6)-C(1)	120.3(2)
C(5)-C(6)-C(7)	131.4(2)
C(1)-C(6)-C(7)	108.37(12)
C(8)-C(7)-C(12)	120.7(2)
C(8)-C(7)-C(6)	129.82(14)
C(12)-C(7)-C(6)	109.47(12)
C(7)-C(8)-C(9)	118.6(2)
C(10)-C(9)-C(8)	121.2(2)
C(9)-C(10)-C(11)	120.8(2)
C(12)-C(11)-C(10)	119.0(2)
C(11)-C(12)-C(7)	119.72(13)
C(11)-C(12)-C(13)	132.82(13)
C(7)-C(12)-C(13)	107.46(13)
N(1)-C(13)-C(1)	121.31(13)
N(1)-C(13)-C(12)	133.04(13)
C(1)-C(13)-C(12)	105.63(11)
N(1)-C(14)-C(15)	113.18(13)
O(1)-C(15)-N(2)	122.91(13)
O(1)-C(15)-C(14)	120.74(14)
N(2)-C(15)-C(14)	116.31(12)
N(2)-C(16)-C(17)	111.22(12)
O(2)-C(17)-O(3)	125.3(2)
O(2)-C(17)-C(16)	125.00(14)
O(3)-C(17)-C(16)	109.71(12)
O(3)-C(18)-C(19)	106.99(13)

Symmetry transformations used to generate equivalent atoms:

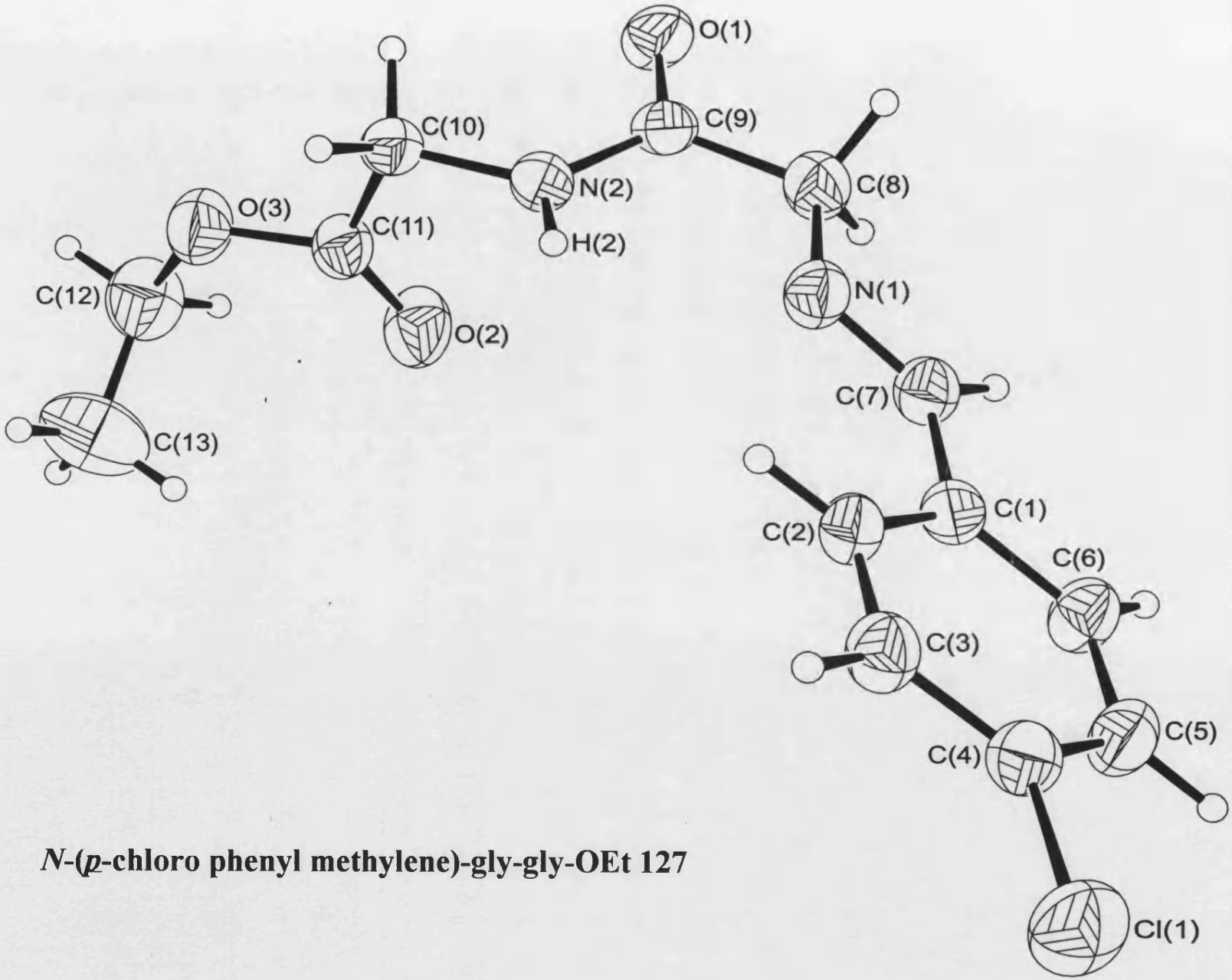
Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for 1.
The anisotropic displacement factor exponent takes the form:
$-2\ pi^2\ [\ h^2\ a^*\ 2\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12\ ]$

Atom	U11	U22	U33	U23	U13	U12
N(1)	44(1)	43(1)	42(1)	2(1)	-4(1)	1(1)
N(2)	45(1)	41(1)	48(1)	2(1)	-11(1)	-1(1)
O(1)	56(1)	51(1)	64(1)	3(1)	-20(1)	-8(1)
O(2)	69(1)	54(1)	67(1)	-3(1)	-13(1)	-6(1)
O(3)	62(1)	37(1)	58(1)	3(1)	1(1)	1(1)
C(1)	38(1)	45(1)	38(1)	3(1)	2(1)	-2(1)
C(2)	52(1)	48(1)	47(1)	-3(1)	0(1)	0(1)
C(3)	61(1)	62(1)	54(1)	-10(1)	4(1)	-12(1)
C(4)	55(1)	79(1)	47(1)	-5(1)	-4(1)	-17(1)
C(5)	42(1)	74(1)	48(1)	11(1)	-5(1)	-2(1)
C(6)	35(1)	54(1)	40(1)	8(1)	3(1)	0(1)
C(7)	40(1)	47(1)	45(1)	11(1)	8(1)	4(1)
C(8)	51(1)	60(1)	62(1)	18(1)	6(1)	14(1)
C(9)	70(1)	44(1)	78(1)	14(1)	18(1)	19(1)
C(10)	68(1)	40(1)	68(1)	4(1)	17(1)	2(1)
C(11)	52(1)	41(1)	53(1)	3(1)	8(1)	-1(1)
C(12)	38(1)	39(1)	42(1)	7(1)	7(1)	1(1)
C(13)	37(1)	40(1)	38(1)	4(1)	4(1)	0(1)
C(14)	48(1)	40(1)	47(1)	4(1)	-7(1)	-2(1)
C(15)	41(1)	44(1)	41(1)	2(1)	0(1)	-1(1)
C(16)	47(1)	43(1)	55(1)	7(1)	-4(1)	2(1)
C(17)	46(1)	44(1)	42(1)	-3(1)	4(1)	5(1)
C(18)	69(1)	33(1)	66(1)	-5(1)	16(1)	0(1)
C(19)	79(1)	38(1)	70(1)	6(1)	12(1)	6(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

Atom, x, y, z, U(eq)

H(2)	8142(1)	3672(1)	8005(1)	57(5)
H(2A)	10538(2)	3997(2)	9641(1)	60
H(3)	12246(2)	4746(2)	10615(1)	72
H(4)	14014(2)	3235(2)	11213(1)	74
H(5)	14106(2)	927(2)	10852(1)	67
H(8)	13721(2)	-1574(2)	10237(1)	70
H(9)	12960(2)	-3547(2)	9571(1)	76
H(10)	10913(2)	-3479(2)	8677(1)	69
H(11)	9584(2)	-1416(2)	8399(1)	58
H(14A)	7767(2)	368(2)	8345(1)	56
H(14B)	8956(2)	590(2)	7843(1)	56
H(16A)	5520(2)	4336(2)	7313(1)	59
H(16B)	6457(2)	3922(2)	6725(1)	59
H(18A)	7859(2)	8115(2)	6682(1)	67
H(18B)	6745(2)	8390(2)	7220(1)	67
H(19A)	5937(10)	9672(2)	6199(4)	94
H(19B)	4718(2)	8530(12)	6271(4)	94
H(19C)	5854(10)	8307(10)	5744(1)	94



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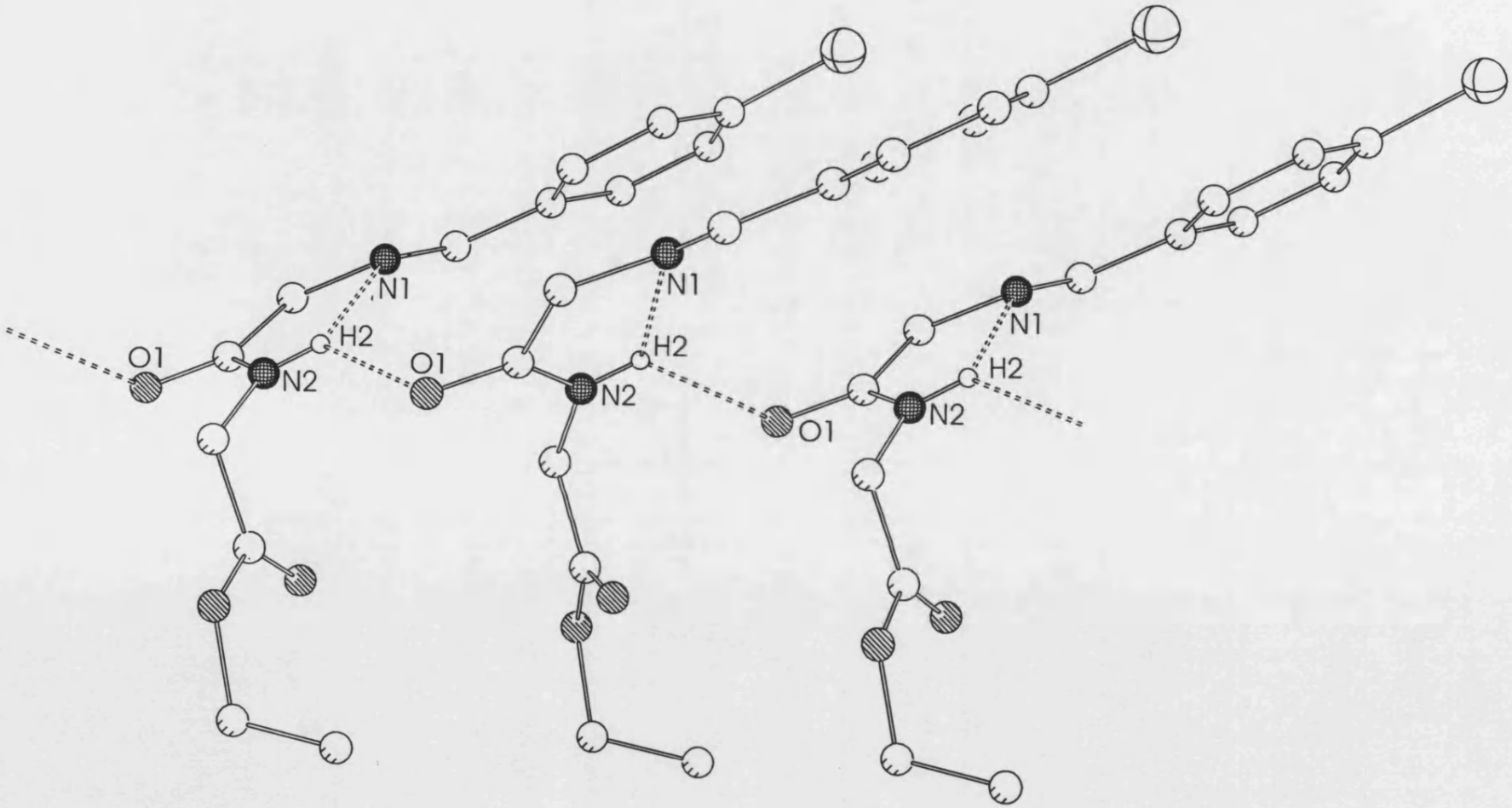
_N_-(_p_-chloro phenyl methylene)-gly-gly-OEt 127



NOTE ON 98jmjw5/d.holland(2)

A crystal of approximate dimensions 0.18 x 0.2 x 0.32 mm was used for data collection.

Crystal data: **$C_{13}H_{15}ClN_2O_3$, *M* = 282.72, Orthorhombic , *a* = 14.7550(10), *b* = 8.4730(10), *c* = 22.726(2) Å ,** $\alpha = 90$, $\beta = 90$, $\gamma = 90^{o}$, $U = 2841.2(5)$ Å^3, space group *Pbca*, $Z = 8$, $D_c = 1.322$ gcm^{-3}, μ(Mo-K$_\alpha$) = 0.274 mm^{-1}, $F(000) = 1184$. Crystallographic measurements were made at 293(2) *K* on a CAD4 automatic four-circle diffractometer in the range $2.26<\theta<24.97^{o}$. Data (2504 reflections) were corrected for Lorentz and polarization and also for extinction.

In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions where relevant.

There are 2 possible, albeit weak, hydrogen-bonding contacts in this crystal structure. H2 (attached to N2) may be hydrogen-bonded intramolecularly to N1 and intermolecularly to O1 of the molecule generated via the *1.5-x, 0.5+y, z* transformation. [H2...N1 2.296(2), N2...N1 2.713(2), H2...O1 2.359(2), N2...O1 2.936(2) Å;

N2-H2-N1 109.98(6), N2-H2-O1 124.79(6)^{o}]

The solution of the structure (SHELX86)[1] and refinement (SHELX93)[2] converged to a conventional [i.e. based on 1578 F^2 data with $Fo>4\sigma(Fo)$] *R1* = 0.0402 and *wR2* = 0.1015. Goodness of fit = 1.020. The max. and min. residual densities were 0.199 and -0.165 eÅ^{-3} respectively. The asymmetric unit (shown in Fig. ...), along with the labelling scheme used was produced using ORTEX.[3] Final fractional atomic co-ordinates and isotropic thermal parameters, bond distances and angles are given in Tables ... , ... and ... respectively. Tables of anisotropic temperature factors are available as supplementary data.

1. Sheldrick G.M., Acta Cryst., A46, 467-73, 1990.

2. Sheldrick G.M., SHELXL, a computer program for crystal structure refinement, University of Göttingen, 1993.

3. McArdle P., J.Appl.Cryst., 28, 65, 1995

Table 1. Crystal data and structure refinement for 1.

Identification code	98jmjw5/d.holland(2)
Empirical formula	$C_{13}H_{15}ClN_2O_3$
Formula weight	282.72
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	a = 14.7550(10)Å $\alpha = 90^\circ$
	b = 8.4730(10)Å $\beta = 90^\circ$
	c = 22.726(2)Å $\gamma = 90^\circ$
Volume	2841.2(5) $Å^3$
Z	8
Density (calculated)	1.322 Mg/m^3
Absorption coefficient	0.274 mm^{-1}
F(000)	1184
Crystal size	0.18 x 0.2 x 0.32 mm
Theta range for data collection	2.26 to 24.97 °.
Index ranges	0<=h<=16; 0<=k<=9; -26<=l<=0
Reflections collected	2504
Independent reflections	2472 [R(int) = 0.0014]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2470 / 0 / 174
Goodness-of-fit on F^2	1.020
Final R indices [$I>2\sigma(I)$]	R1 = 0.0402 wR2 = 0.1015
R indices (all data)	R1 = 0.0733 wR2 = 0.1126
Largest diff. peak and hole	0.199 and -0.165 $eÅ^{-3}$
Weighting scheme	calc $w=1/[\sigma^2(Fo^2)+(0.0557P)^2+0.2797P]$ where $P=(Fo^2+2Fc^2)/3$
Extinction coefficient	0.0036(7)
Extinction expression	$Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
Cl(1)	6114(1)	1413(1)	4530(1)	94(1)
N(1)	6210(1)	-5670(2)	3164(1)	60(1)
N(2)	7384(1)	-7115(2)	2419(1)	54(1)
O(1)	6500(1)	-9257(2)	2323(1)	73(1)
O(2)	7211(1)	-6412(2)	1240(1)	90(1)
O(3)	8622(1)	-7259(2)	1066(1)	81(1)
C(1)	5735(1)	-3187(2)	3570(1)	52(1)
C(2)	6592(1)	-2671(3)	3729(1)	57(1)
C(3)	6711(2)	-1257(3)	4017(1)	63(1)
C(4)	5966(2)	-354(3)	4145(1)	62(1)
C(5)	5107(2)	-819(3)	3987(1)	68(1)
C(6)	4998(1)	-2234(3)	3700(1)	65(1)
C(7)	5588(1)	-4723(3)	3290(1)	58(1)
C(8)	5945(2)	-7194(3)	2920(1)	67(1)
C(9)	6638(1)	-7935(2)	2529(1)	53(1)
C(10)	8064(1)	-7610(2)	2010(1)	57(1)
C(11)	7895(2)	-7012(3)	1407(1)	61(1)
C(12)	8542(2)	-6902(4)	440(1)	98(1)
C(13)	8752(3)	-5260(5)	323(2)	138(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

Cl(1)-C(4)	1.747(2)
N(1)-C(7)	1.253(3)
N(1)-C(8)	1.459(3)
N(2)-C(9)	1.325(2)
N(2)-C(10)	1.432(2)
O(1)-C(9)	1.231(2)
O(2)-C(11)	1.193(2)
O(3)-C(11)	1.339(3)
O(3)-C(12)	1.459(3)
C(1)-C(2)	1.386(3)
C(1)-C(6)	1.386(3)
C(1)-C(7)	1.465(3)
C(2)-C(3)	1.376(3)
C(3)-C(4)	1.372(3)
C(4)-C(5)	1.374(3)
C(5)-C(6)	1.375(3)
C(8)-C(9)	1.493(3)
C(10)-C(11)	1.482(3)
C(12)-C(13)	1.449(5)
C(7)-N(1)-C(8)	117.2(2)
C(9)-N(2)-C(10)	123.4(2)
C(11)-O(3)-C(12)	117.8(2)
C(2)-C(1)-C(6)	118.4(2)
C(2)-C(1)-C(7)	121.9(2)
C(6)-C(1)-C(7)	119.6(2)
C(3)-C(2)-C(1)	121.0(2)
C(4)-C(3)-C(2)	119.0(2)
C(3)-C(4)-C(5)	121.5(2)
C(3)-C(4)-Cl(1)	119.0(2)
C(5)-C(4)-Cl(1)	119.5(2)
C(4)-C(5)-C(6)	118.9(2)
C(5)-C(6)-C(1)	121.1(2)
N(1)-C(7)-C(1)	124.0(2)
N(1)-C(8)-C(9)	114.5(2)
O(1)-C(9)-N(2)	122.9(2)
O(1)-C(9)-C(8)	119.7(2)
N(2)-C(9)-C(8)	117.4(2)
N(2)-C(10)-C(11)	112.5(2)
O(2)-C(11)-O(3)	124.2(2)
O(2)-C(11)-C(10)	125.5(2)
O(3)-C(11)-C(10)	110.3(2)
C(13)-C(12)-O(3)	111.1(3)

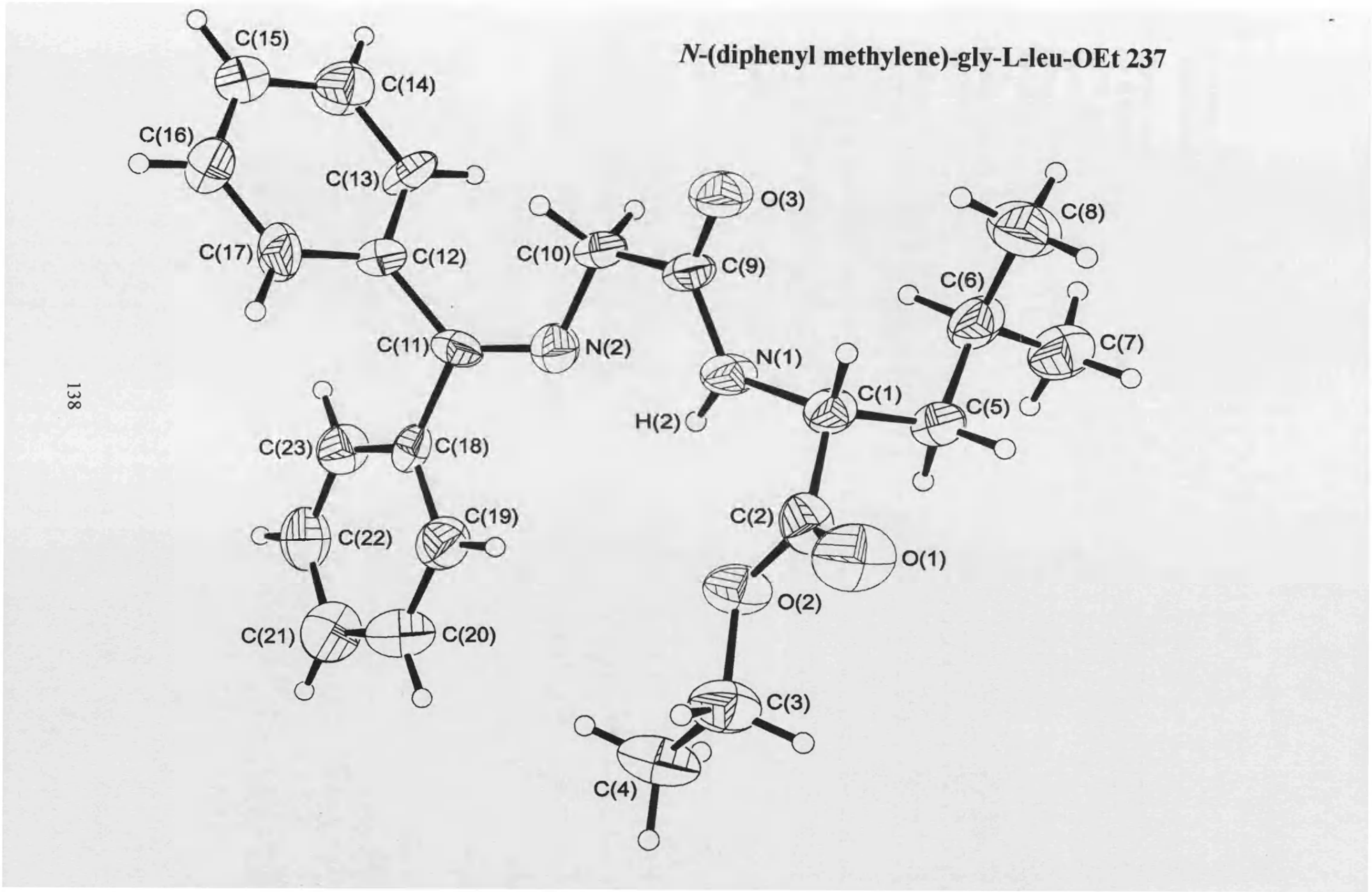
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for 1.
The anisotropic displacement factor exponent takes the form:
$-2\ pi^2\ [\ h^2\ a^*\ 2\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12\ ]$

Atom	U11	U22	U33	U23	U13	U12
Cl(1)	100(1)	81(1)	100(1)	-32(1)	7(1)	-5(1)
N(1)	53(1)	59(1)	69(1)	-7(1)	6(1)	-3(1)
N(2)	53(1)	45(1)	64(1)	-3(1)	3(1)	-5(1)
O(1)	61(1)	46(1)	111(1)	-10(1)	2(1)	-5(1)
O(2)	57(1)	127(2)	85(1)	19(1)	-6(1)	8(1)
O(3)	68(1)	100(1)	74(1)	5(1)	12(1)	10(1)
C(1)	49(1)	57(1)	51(1)	5(1)	2(1)	2(1)
C(2)	48(1)	63(1)	62(1)	3(1)	8(1)	4(1)
C(3)	53(1)	69(2)	68(1)	-6(1)	3(1)	-5(1)
C(4)	70(2)	61(1)	54(1)	-3(1)	6(1)	0(1)
C(5)	58(1)	70(2)	76(2)	-6(1)	9(1)	13(1)
C(6)	48(1)	69(2)	76(2)	-8(1)	0(1)	5(1)
C(7)	47(1)	63(1)	64(1)	1(1)	0(1)	-2(1)
C(8)	64(1)	59(1)	77(2)	-4(1)	11(1)	-7(1)
C(9)	51(1)	44(1)	64(1)	5(1)	-6(1)	1(1)
C(10)	51(1)	47(1)	74(1)	3(1)	3(1)	1(1)
C(11)	47(1)	64(2)	73(2)	-2(1)	0(1)	-6(1)
C(12)	102(2)	120(3)	73(2)	-5(2)	6(2)	4(2)
C(13)	188(4)	118(3)	108(3)	28(2)	-11(3)	-24(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

Atom	x	y	z	U(eq)
H(2)	7463(1)	-6239(2)	2603(1)	65
H(2A)	7094(1)	-3291(3)	3641(1)	69
H(3)	7289(2)	-919(3)	4122(1)	76
H(5)	4609(2)	-188(3)	4073(1)	81
H(6)	4420(1)	-2558(3)	3591(1)	77
H(7)	4996(1)	-5014(3)	3201(1)	69
H(8A)	5389(2)	-7057(3)	2697(1)	80
H(8B)	5816(2)	-7911(3)	3242(1)	80
H(10A)	8083(1)	-8755(2)	2000(1)	69
H(10B)	8651(1)	-7238(2)	2143(1)	69
H(12A)	8953(2)	-7571(4)	219(1)	118
H(12B)	7930(2)	-7128(4)	310(1)	118
H(13A)	8722(17)	-5068(9)	-93(2)	207
H(13B)	9351(7)	-5027(9)	463(11)	207
H(13C)	8321(11)	-4598(5)	522(9)	207


N-(diphenyl methylene)-gly-L-leu-OEt 237
C(15)
C(14)
C(16)
C(13)
C(17)
C(12)
C(10)
O(3)
C(9)
C(8)
C(6)
C(7)
C(11)
N(2)
N(1)
C(1)
C(5)
H(2)
C(23)
C(18)
C(2)
C(19)
C(22)
O(1)
O(2)
C(21)
C(20)
C(3)
C(4)

NOTE ON 98JMJW3

A crystal of approximate dimensions 0.4 x 0.25 x 0.6 mm was used for data collection.

Crystal data: $C_{23}\ H_{26}\ N_2\ O_3$, M = 380.47, Monoclinic , a = 5.255(2), b = 21.926(2), c = 9.623 (2) Å , β = 104.06(2)°, U = 1075.6(5) Å^3, space group $P2_1/c$, Z = 2, D_c = 1.175 gcm^{-3}, μ(Mo-K_α) = 0.078 mm^{-1}, F(000) = 480. Crystallographic measurements were made at 293(2)° K on a CAD4 automatic four-circle diffractometer in the range 2.18<θ<23.98°. Data (1982 reflections) were corrected for Lorentz and polarization and also for extinction.

In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions where relevant.

The solution of the structure (SHELX86)[1] and refinement (SHELX93)[2] converged to a conventional [i.e. based on 2211 F^2 data with $Fo>4\sigma(Fo)$] $R1$ = 0.0877 and $wR2$ = 0.1929. Goodness of fit = 0.807. The max. and min. residual densities were 0.201 and -0.870 eÅ^{-3} respectively. The asymmetric unit (shown in Fig. ...), along with the labelling scheme used was produced using ORTEX.[3] Final fractional atomic co-ordinates and isotropic thermal parameters, bond distances and angles are given in Tables ... , ... and ... respectively. Tables of anisotropic temperature factors are available as supplementary data.

1. Sheldrick G.M., Acta Cryst., A46, 467-73, 1990.

2. Sheldrick G.M., SHELXL, a computer program for crystal structure refinement, University of Göttingen, 1993.

McArdle P., J.Appl.Cryst., 28, 65, 1995

Table 1. Crystal data and structure refinement for 1.

Identification code	98jmjw3
Empirical formula	$C_{23} H_{28} N_2 O_3$
Formula weight	380.47
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 5.255(2)Å b = 21.926(5)Å β = 104.06(2)° c = 9.623(2)Å
Volume	1075.6(5) $Å^3$
Z	2
Density (calculated)	1.175 Mg/m^3
Absorption coefficient	0.078 mm^{-1}
F(000)	408
Crystal size	0.4 x 0.25 x 0.6 mm
Theta range for data collection	2.18 to 23.98 °.
Index ranges	0<=h<=6; 0<=k<=25; -10<=l<=10
Reflections collected	1982
Independent reflections	1714 [R(int) = 0.0220]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1704 / 1 / 257
Goodness-of-fit on F^2	0.793
Final R indices [I>2σ(I)]	R1 = 0.0877 wR2 = 0.1929
R indices (all data)	R1 = 0.1981 wR2 = 0.2769
Absolute structure parameter	10(10)
Largest diff. peak and hole	0.284 and -0.250 $eÅ^{-3}$
Weighting scheme	calc $w=1/[\sigma^2(Fo^2)+(0.1447P)^2]$ where $P=(Fo^2+2Fc^2)/3$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
N(1)	-3324(17)	-619(4)	-11168(9)	64(3)
N(2)	295(18)	-1474(4)	-10926(9)	67(3)
O(1)	-7826(18)	55(6)	-9387(9)	104(3)
O(2)	-3776(14)	-314(5)	-8548(8)	73(2)
O(3)	-5632(16)	-959(5)	-13326(8)	76(2)
C(1)	-5119(19)	-120(5)	-11037(10)	57(3)
C(2)	-5785(23)	-128(5)	-9604(12)	67(3)
C(3)	-4053(25)	-247(7)	-7128(12)	88(4)
C(4)	-1539(28)	-424(7)	-6133(13)	108(5)
C(5)	-4039(24)	499(5)	-11225(11)	70(3)
C(6)	-3298(24)	608(6)	-12643(13)	77(4)
C(7)	-1725(28)	1185(7)	-12585(15)	97(4)
C(8)	-5686(25)	625(8)	-13902(13)	107(5)
C(9)	-3659(22)	-966(5)	-12309(11)	56(3)
C(10)	-1451(22)	-1404(5)	-12333(10)	64(3)
C(11)	1521(20)	-1977(6)	-10584(10)	53(3)
C(12)	1421(22)	-2516(5)	-11517(11)	62(3)
C(13)	2352(23)	-2481(5)	-12751(12)	73(4)
C(14)	2243(25)	-2973(7)	-13633(14)	86(4)
C(15)	1150(27)	-3523(6)	-13350(14)	82(4)
C(16)	238(29)	-3554(6)	-12102(15)	94(4)
C(17)	402(24)	-3063(6)	-11223(14)	79(4)
C(18)	3176(21)	-2052(4)	-9083(12)	53(3)
C(19)	2541(25)	-1751(5)	-7961(14)	78(4)
C(20)	4010(29)	-1829(7)	-6590(15)	89(4)
C(21)	6158(27)	-2181(7)	-6258(17)	92(4)
C(22)	6770(26)	-2461(6)	-7386(18)	88(4)
C(23)	5354(23)	-2404(5)	-8777(15)	69(3)

Table 3. Bond lengths [Å] and angles [°] for 1.

N(1)-C(9)	1.311(12)
N(1)-C(1)	1.469(13)
N(2)-C(11)	1.280(13)
N(2)-C(10)	1.447(12)
O(1)-C(2)	1.210(12)
O(2)-C(2)	1.339(12)
O(2)-C(3)	1.417(12)
O(3)-C(9)	1.241(11)
C(1)-C(2)	1.503(14)
C(1)-C(5)	1.50(2)
C(3)-C(4)	1.48(2)
C(5)-C(6)	1.53(2)
C(6)-C(8)	1.518(14)
C(6)-C(7)	1.50(2)
C(9)-C(10)	1.511(14)
C(11)-C(12)	1.48(2)
C(11)-C(18)	1.503(14)
C(12)-C(17)	1.371(14)
C(12)-C(13)	1.392(14)
C(13)-C(14)	1.37(2)
C(14)-C(15)	1.39(2)
C(15)-C(16)	1.40(2)
C(16)-C(17)	1.36(2)
C(18)-C(23)	1.353(13)
C(18)-C(19)	1.374(14)
C(19)-C(20)	1.37(2)
C(20)-C(21)	1.34(2)
C(21)-C(22)	1.35(2)
C(22)-C(23)	1.37(2)
C(9)-N(1)-C(1)	123.0(8)
C(11)-N(2)-C(10)	119.8(9)
C(2)-O(2)-C(3)	117.0(9)
N(1)-C(1)-C(2)	111.5(9)
N(1)-C(1)-C(5)	113.2(9)
C(2)-C(1)-C(5)	107.5(8)
O(1)-C(2)-O(2)	122.6(10)
O(1)-C(2)-C(1)	124.6(10)
O(2)-C(2)-C(1)	112.6(9)
O(2)-C(3)-C(4)	108.1(10)
C(1)-C(5)-C(6)	115.9(9)
C(8)-C(6)-C(7)	110.4(13)

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for 1.
The anisotropic displacement factor exponent takes the form:
$-2\ pi^2\ [\ h^2\ a^*\ 2\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12\ ]$

Atom	U11	U22	U33	U23	U13	U12
N(1)	55(6)	81(7)	46(5)	-12(5)	-9(4)	23(5)
N(2)	70(7)	60(7)	67(6)	-1(5)	10(5)	10(6)
O(1)	61(5)	151(9)	105(6)	-11(6)	29(5)	32(6)
O(2)	57(5)	110(7)	61(5)	-4(5)	28(4)	9(5)
O(3)	73(6)	91(6)	55(5)	-14(4)	-3(4)	7(5)
C(1)	50(7)	61(8)	53(6)	-10(6)	2(5)	7(6)
C(2)	46(7)	73(8)	82(8)	13(7)	19(7)	20(7)
C(3)	81(9)	121(12)	66(8)	-5(8)	27(8)	9(8)
C(4)	105(11)	163(15)	54(7)	-2(8)	13(8)	-17(10)
C(5)	83(9)	68(8)	54(7)	-12(6)	10(6)	9(7)
C(6)	74(9)	75(9)	81(9)	-20(7)	17(7)	21(8)
C(7)	103(11)	103(11)	91(10)	-18(8)	37(9)	7(10)
C(8)	103(11)	135(13)	71(9)	-2(9)	0(8)	17(11)
C(9)	67(8)	60(7)	41(6)	-14(6)	16(6)	-2(7)
C(10)	80(8)	65(7)	42(6)	-16(6)	6(6)	2(7)
C(11)	55(7)	71(8)	34(6)	3(6)	12(5)	-14(7)
C(12)	81(8)	60(8)	43(7)	-11(6)	11(6)	1(7)
C(13)	92(9)	58(8)	73(8)	-36(7)	23(7)	-15(7)
C(14)	90(10)	96(12)	81(9)	-12(9)	37(8)	9(9)
C(15)	111(11)	71(9)	61(8)	-8(7)	12(8)	-9(8)
C(16)	128(12)	54(8)	89(11)	-6(8)	4(9)	0(8)
C(17)	106(10)	51(8)	89(9)	13(7)	42(8)	-14(7)
C(18)	55(7)	35(6)	72(8)	-5(6)	22(6)	-7(6)
C(19)	81(10)	70(9)	79(9)	-7(7)	10(8)	0(7)
C(20)	78(10)	120(12)	69(9)	-19(8)	18(8)	-7(9)
C(21)	62(9)	97(11)	104(12)	-5(9)	-4(8)	5(9)
C(22)	72(10)	73(9)	118(13)	15(9)	23(9)	18(7)
C(23)	59(7)	72(9)	78(9)	-3(7)	18(7)	13(7)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

Atom	x	y	z	U(eq)
H(1)	-1993(17)	-686(4)	-10464(9)	77
H(2)	-6747(19)	-175(5)	-11781(10)	68
H(3A)	-5459(25)	-506(7)	-6978(12)	106
H(3B)	-4477(25)	172(7)	-6957(12)	106
H(4A)	-1686(71)	-382(43)	-5163(13)	162
H(4B)	-162(47)	-163(31)	-6285(74)	162
H(4C)	-1139(99)	-840(16)	-6308(73)	162
H(5A)	-2494(24)	565(5)	-10452(11)	84
H(5B)	-5331(24)	802(5)	-11129(11)	84
H(6)	-2191(24)	268(6)	-12796(13)	93
H(7A)	-207(101)	1164(19)	-11795(64)	145
H(7B)	-2782(65)	1528(8)	-12461(103)	145
H(7C)	-1180(161)	1230(24)	-13462(44)	145
H(8A)	-6457(113)	226(13)	-14050(66)	160
H(8B)	-5165(41)	751(43)	-14747(26)	160
H(8C)	-6945(87)	909(34)	-13704(46)	160
H(10A)	-2179(22)	-1798(5)	-12675(10)	76
H(10B)	-464(22)	-1255(5)	-12994(10)	76
H(13)	3060(23)	-2116(5)	-12978(12)	88
H(14)	2913(25)	-2940(7)	-14439(14)	103
H(15)	1031(27)	-3855(6)	-13963(14)	99
H(16)	-491(29)	-3915(6)	-11872(15)	113
H(17)	-196(24)	-3100(6)	-10393(14)	95
H(19)	1097(25)	-1492(5)	-8135(14)	94
H(20)	3494(29)	-1627(7)	-5853(15)	107
H(21)	7151(27)	-2229(7)	-5323(17)	110
H(22)	8250(26)	-2709(6)	-7205(18)	105
H(23)	5888(23)	-2607(5)	-9507(15)	83

C(8)-C(6)-C(5)	112.1(11)
C(7)-C(6)-C(5)	110.9(10)
O(3)-C(9)-N(1)	124.7(11)
O(3)-C(9)-C(10)	119.5(10)
N(1)-C(9)-C(10)	115.7(10)
N(2)-C(10)-C(9)	111.5(9)
N(2)-C(11)-C(12)	126.3(9)
N(2)-C(11)-C(18)	118.6(10)
C(12)-C(11)-C(18)	115.0(10)
C(17)-C(12)-C(13)	117.4(10)
C(17)-C(12)-C(11)	122.2(10)
C(13)-C(12)-C(11)	120.4(10)
C(14)-C(13)-C(12)	121.0(11)
C(13)-C(14)-C(15)	121.4(11)
C(14)-C(15)-C(16)	117.0(12)
C(17)-C(16)-C(15)	120.9(12)
C(16)-C(17)-C(12)	122.2(12)
C(23)-C(18)-C(19)	117.2(11)
C(23)-C(18)-C(11)	122.2(11)
C(19)-C(18)-C(11)	120.6(11)
C(20)-C(19)-C(18)	120.7(12)
C(21)-C(20)-C(19)	123.2(13)
C(20)-C(21)-C(22)	114.9(13)
C(21)-C(22)-C(23)	124.3(13)
C(18)-C(23)-C(22)	119.6(12)

Symmetry transformations used to generate equivalent atoms: